FACULTY OF MEDICINE AND HEALTH SCIENCES
DEPARTMENT OF REHABILITATION SCIENCES AND PHYSIOTHERAPY

Neural correlates of visual-motor disorders in children with developmental coordination disorder

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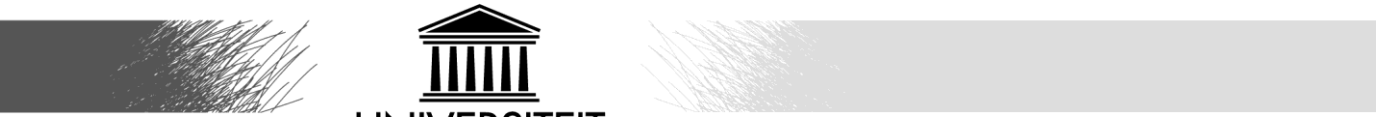

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Contents

List of publications used in this thesis

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Debrabant, J., Gheysen, F., Caeyenberghs, K., Van Waelvelde, H., & Vingerhoets, G. (2013). Neural underpinnings of impaired predictive motor timing in children with Developmental Coordination Disorder. Research in Developmental Disabilities, 34(5), 1478-1487.

Summary

Developmental coordination disorder (DCD) refers to a neuromotor developmental disorder that affects approximately 1.8% of school-aged children.[1] DCD interferes with a child's performance of daily and school activities that require coordinated movement, including writing, computer skills, personal care and sports.[2] Children with DCD typically experience difficulties with fine and/or gross motor abilities.[2] Besides, DCD is frequently diagnosed in children with other developmental disorders, including attention deficit hyperactivity disorder, autism spectrum disorder, and learning disabilities.[1]

Although neuroimaging research on DCD has extended in recent years, the neuropathology remains poorly understood.[3] That is why diagnostics of DCD are mainly based on anamnesis and norm referenced clinical motor performance, together with a neurological examination to exclude possible medical causes according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition criteria.[2] Because specific neurobiological markers of DCD are currently lacking, the administration of magnetic resonance imaging (MRI) scans is not a standard procedure. Even though neuroimaging data is currently insufficient, substantial and widespread differences in brain structure and function have been denoted in children with DCD.[3] This project aimed to extend initial findings on brain features that associate with DCD-related visual-motor problems. This objective was achieved through connecting data from behavioural visual-motor tests and multiple MRI modalities (diffusion tensor imaging (DTI) and functional MRI) in groups of children with DCD and matched typically developing children.

Visual-motor skills were found to progressively develop in children between 5 to 12 years of age using the Beery-Buktenica Developmental Test of Visual Motor Integration (Beery VMI),[4] confirming this clinical test's validity. A similar developmental trajectory was demonstrated in children's simple visual-motor reaction time (RT) performance at predictive (i.e., regularly paced) and unpredictive (i.e., irregularly paced) stimuli. RT indices of motor timing and processing speed discriminated well between age groups and were predictive of Beery VMI outcomes.

Both specific structural white matter alterations and disrupted network topology associated with visual-motor deficits in children with DCD indicate possible clinical applications of DTI and network metrics for diagnostic and prognostic purposes. Specifically, lower fractional anisotropy values were detected in the retrolenticular limb of the internal capsule, suggesting deficient myelination. Graph theoretical network analyses denoted a weaker structural network segregation and integration

reflected by decreases in clustering coefficient, global and local efficiency in children with DCD compared to controls. Moreover, significant correlations between DTI/network metrics and visual-motor Beery VMI tracing outcomes supported brain-behavioural associations.

Task-related activation from functional MRI suggested impaired predictive visual-motor control in children with DCD. Unlike children with DCD, typically developing children exhibited decreased activation in the right dorsolateral prefrontal cortex and right inferior frontal gyrus, indicating facilitated and speeded responding at predictive as opposed to unpredictive stimuli. Instead, activation patterns did not differ in children with DCD, which suggests compensatory processing due to poor predictive encoding.

In conclusion, DCD in children affects the brain's structural and functional connectivity with such properties that associate with deficient visual-motor skills. The presented findings demonstrate the potential clinical value of incorporating MRI based methods in diagnostic procedures of DCD and related visual-motor disorders.

Samenvatting

Developmental coordination disorder (DCD) verwijst naar een neuromotorische ontwikkelingsstoornis die voorkomt bij ongeveer 1.8% van de schoolgaande kinderen.[1] DCD beïnvloedt de gecoördineerde uitvoering van dagdagelijkse en schoolse activiteiten van het kind, zoals schrijf- en computervaardigheden, persoonlijke lichaamsverzorging en sport.[2] Kinderen met DCD worden gekenmerkt door moeilijkheden met fijn- en/of grofmotorische vaardigheden. Daarnaast wordt DCD ook frequent gediagnosticeerd samen met andere ontwikkelingsstoornissen zoals attention deficit hyperactivity disorder, autismespectrumstoornis en leerstoornissen.[1]

De neuropathologie van DCD is nauwelijks gekend, hoewel beeldvormingsonderzoek de laatste jaren is toegenomen.[3] Momenteel gebeurt de diagnosestelling van DCD voornamelijk op basis van anamnese en prestaties op genormeerde klinisch motorische testen, evenals een neurologisch onderzoek om mogelijke medische oorzaken uit te sluiten. Deze diagnostische procedure volgt de criteria van de Diagnostic and Statistical Manual of Mental Disorders, 5th edition.[2] Aangezien er nog geen specifieke neurologische markers voor DCD getraceerd zijn, is er standaard geen afname van magnetische resonante beeldvorming (MRI) scans. Desondanks duidt de beeldvormingsdata op significante en wijdverspreide verschillen in hersenstructuur en -functie bij kinderen met DCD.[3] Dit project beoogde het uitbreiden van de initiële bevindingen omtrent hersensystemen geassocieerd met visueel-motorische stoornissen gerelateerd met DCD. Deze doelstelling werd bereikt door resultaten op visueel-motorische gedragstesten in verband te brengen met MRI data (diffusion tensor imaging (DTI) en functionele MRI) van kinderen met DCD in vergelijking met typisch ontwikkelende kinderen.

Er werd een progressieve ontwikkeling van visueel-motorische vaardigheden vastgesteld bij typisch ontwikkelende kinderen tussen 5 en 12 jaar door middel van de klinisch gevalideerde Beery-Buktenica Developmental Test of Visual Motor Integration (Beery VMI).[4] Deze kinderen vertoonden een vergelijkbaar ontwikkelingstraject voor visueel-motorische reactietijden (RT) op temporeel regelmatige en onregelmatige stimuli. Ook konden afgeleide RT indices voor motorische timing en verwerkingssnelheid discrimineren tussen leeftijdsgroepen, alsook significant bijdragen in de predictie van Beery VMI scores.

Specifieke veranderingen in witte stof en netwerk topologie correleerden met visueel-motorische beperkingen bij kinderen met DCD. Deze correlaties wijzen op de mogelijke klinische toepassingen van DTI en netwerk uitkomstmaten voor diagnosestelling. Meer bepaald wijzen lagere fractionele

anisotropie in het retrolentiform deel van de capsula interna op een afwijkende myelinisatie. Tevens suggereren graph theoretische analyses een zwakkere structurele netwerk segregatie en integratie omwille van een verlaagde cluster coëfficiënt, globale en lokale efficiëntie bij kinderen met DCD in vergelijking met controles. Deze hersengedragrelaties werden bevestigd via significante correlaties tussen DTI/netwerk en visueel-motorische uitkomstmaten.

Taak-gerelateerde functionele MRI activatie impliceerde gestoorde predictieve visueel-motorische controle bij kinderen met DCD. In tegenstelling tot kinderen met DCD, vertoonden typisch ontwikkelende kinderen minder activatie in de rechter dorsolaterale prefrontale cortex en rechter inferieure frontale gyrus, gepaard met gefaciliteerde en snellere responsen op regelmatige in vergelijking met onregelmatige stimuli. Dergelijke activatieverschillen waren afwezig bij kinderen met DCD, mogelijk door zwakke predictieve encoderingsvaardigheden met compensatoire activatie tot gevolg.

We kunnen besluiten dat kinderen met DCD een verstoorde hersenstructuur en – functie vertonen, die geassocieerd is met afwijkende visueel-motorische vaardigheden. Deze bevindingen suggereren klinische toepassingsmogelijkheden van geïntegreerde MRI afnames in de diagnosestelling van DCD en gerelateerde visueel-motorische stoornissen.

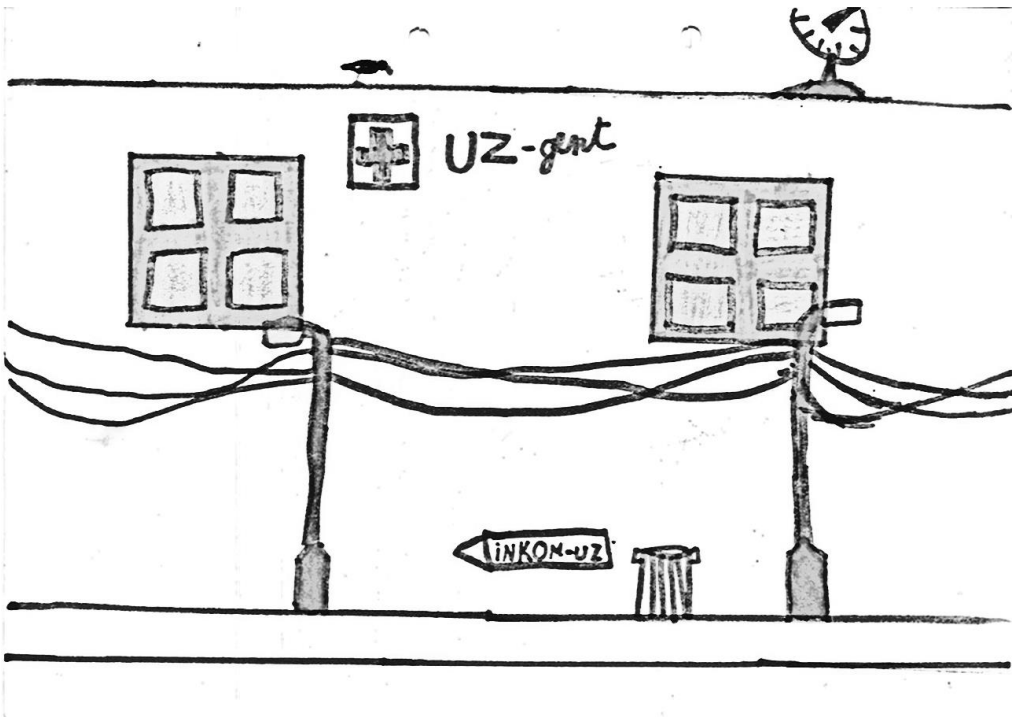
Abbreviations

AAL	Anatomical automatic labeling atlas
AD	Axial diffusivity
ADHD	Attention deficit hyperactivity disorder
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APA	American Psychiatric Association
AR	Anticipatory response
ADL	Activities of daily living
ASD	Autism spectrum disorder
AUC	Area under the receiver operating characteristic curve
BA	Brodmann area
Beery VMI	Beery-Buktenica Developmental Test of Visual-Motor Integration
BOLD	Blood oxygen level dependent
BOT	Bruininks-Oseretsky Test of Motor Proficiency
CP	Cerebral palsy
CT	Computed tomography
DCD	Developmental coordination disorder
DCD-Q	Developmental Coordination Disorder Questionnaire
DLPFC	Dorsolateral prefrontal gyrus
DSM	Diagnostic and Statistical Manual of Mental Disorders
DTI	Diffusion tensor imaging
EACD	European Academy for Childhood Disability
EPI	Echoplanar imaging
FA	Fractional anisotropy
FOV	Field of view
GLM	General linear model
ICF	International classification of functioning, disability, and health
IFG	Inferior frontal gyrus
ISI	Interstimulus interval
IQ	Intelligence quotient
KTK	Körper Koördination Test für Kinder
LMM	Linear mixed model
M	Mean
MABC	Movement Assessment Battery for Children
MD	Mean diffusivity
MR	Magnetic resonance
MRI	Magnetic resonance imaging
NF1	Neurofibromatosis type 1
PANESS	Physical and Neurological Examination for Soft Signs
RD	Radial diffusivity
ROI	Region of interest
RT	Reaction time

SD	Standard deviation
SE	Standard error
SNP	Single-nucleotide polymorphism
TD	Typically developing
TE	Echo time
TGMD	Test for Gross Motor Development
TPJ	Temporo-parietal junction
TR	repetition time
UBO	Unidentified bright object
VMI	Visual-motor integration
VRT	Visual-motor reaction time
WHO	World Health Organization
WISC	Wechsler Intelligence Scale for Children
WM	White matter
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

Chapter 1

General introduction



1 General introduction

1.1 Developmental coordination disorder

Developmental coordination disorder (DCD) is a neurodevelopmental disorder affecting fine and gross motor skills in children and adults. This motor disorder is recognised by international organisations including the American Psychiatric Association (APA)[2] and World Health Organization (WHO)[5]. DCD is distinct from other motor disorders such as cerebral palsy (CP) and muscular dystrophy. High phenotypic variation is found in terms of severity and disposition as DCD may cause impaired sensorimotor coordination, postural control, and/or motor learning.[6] Moreover, DCD is often diagnosed together with other developmental disorders such as attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), or learning disabilities.[2,3] Due to this heterogeneous clinical presentation, uncertainty remains regarding diagnosis, prognosis and pathogenesis of DCD.

The diagnosis of DCD currently relies on descriptive criteria stated in the DSM-5.[2] DCD requires substantial interference of motor coordination problems with academic achievement or activities of daily living. This criterion accords with the International Classification of Functioning, Disability and Health (ICF)[7] focus on the person's/child's actual everyday functioning at different levels of body function and structure (impairments), activity and participation. Children with DCD typically display difficulties with self-care, writing, typing, and sport activities, as well as participation problems with other educational and recreational activities.[8]

Regarding the prognosis of DCD, longitudinal studies found that children with DCD continue to experience difficulties in activities that require motor proficiency throughout adolescence and adulthood.[9] Aside from the motor domain, long-term outcomes indicate that DCD is associated with secondary mental health, emotional, and behavioural issues as well.[9-11] According to parental reports, initial motor and play deficits in the early years generally extend to self-care, academic, and peer problems in middle childhood, and to issues with self-esteem and emotional health in later childhood and adolescence.[11] Children with DCD and co-morbid conditions (e.g., ADHD) have poorer psychosocial outcomes[12] and higher levels of depressive symptoms.[13, 14] DCD also puts children at a higher risk for obesity,[15, 16] and coronary vascular disease due to decreased participation levels in physical activity.[17] Compared to typical peers, they have lower cardiorespiratory and physical fitness[18-22] which may persist with increasing age.[18, 20]

Considering these challenges facing children with DCD, greater attention to identification and diagnosis of DCD is urgently needed to initiate support, education, and intervention for children and their families. ICF provides a useful framework to categorize assessment results and treatment approaches.[7] The integrative dynamics within the ICF suggest further research into the neuropathology of DCD (i.e., the level of body function and structure) to optimize clinical tools for early diagnosis and intervention.

1.1.1 Diagnosis

DCD has gained increasing recognition as a clinically important condition in childhood. Formerly used terms to describe children with clumsy motor behaviour included clumsy child syndrome, minimal brain dysfunction, developmental dyspraxia, and minor neurologic dysfunction.[3] In response to the confusing heterogeneity of these labels, participants at an international multidisciplinary consensus meeting in 1994 agreed to use the term developmental coordination disorder (DCD), as described in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV).[23, 24] In 2013, the diagnostic criteria were further refined with the publication of the DSM-5.[2]

DSM-5 classifies DCD as a discrete motor disorder under the broader heading of neurodevelopmental disorders. The specific DSM-5 criteria for DCD are as follows:

A. Acquisition and execution of coordinated motor skills are below what would be expected at a given chronologic age and opportunity for skill learning and use; difficulties are manifested as clumsiness (e.g., dropping or bumping into objects) and as slowness and inaccuracy of performance of motor skills (e.g., catching an object, using scissors, handwriting, riding a bike, or participating in sports).

B. The motor skills deficit significantly or persistently interferes with activities of daily living appropriate to the chronologic age (e.g., self-care and self-maintenance) and impacts academic/school productivity, prevocational and vocational activities, leisure, and play.

C. The onset of symptoms is in the early developmental period.

D. The motor skills deficits cannot be better explained by intellectual disability or visual impairment and are not attributable to a neurologic condition affecting movement (e.g., cerebral palsy, muscular dystrophy, or a degenerative disorder).

Disordered motor abilities become most evident during the school years, as children face motor challenges such as sportive activities and writing. In some cases, children with motor coordination difficulties present at an early age as indicated by a delayed development of motor milestones (e.g., rolling over, sitting unsupported, walking). Children at risk of DCD may be detected using norm-referenced developmental tests, even before school age.

The European Academy for Childhood Disability (EACD) advised to use reliable and norm-referenced tests and questionnaires in diagnosing DCD.[25] The following tests are frequently used with regard to criteria A and C:

- Movement Assessment Battery for Children - second edition (MABC-2)[26]
- Bruininks-Oseretsky Test of Motor Proficiency - second edition (BOT-2)[27]
- Test for Gross Motor Development - second edition (TGMD-2)[28]

Standardized and norm-referenced questionnaires for evaluating criterium B include the Developmental Coordination Disorder Questionnaire (DCD-Q)[29] for parents and the MABC-2 checklist for teachers.[30]

Criterion D requires a neurologic examination, in conjunction with an assessment that focuses on subtle deficits in neural functioning:

- Touwen test for children with minor neurologic dysfunction[31]
- Physical and Neurological Examination for Soft Signs (PANESS)[32]

A formal intelligence quotient (IQ) test is regularly applied as well to identify intellectual disabilities, for example:

- Wechsler Preschool and Primary Scale of Intelligence - third edition and - fourth edition (WPPSI-III[33] and WPPSI-IV)[34]
- Wechsler Intelligence Scale for Children - third edition and - fourth edition (WISC-III[35] and WISC-IV)[36]
- Snijders-Oomen non-verbal IQ test (SON-R)[37]

The difficulties of DCD are recognized across culture, race, socio-economic status, and gender.[38] Notably, the prevalence of DCD is directly related to which assessment tests are employed and the choice of cut-off points. A population-based study from the United Kingdom used strict inclusion criteria and reported a prevalence for DCD of 1.8%.[1] This contrasts with APA rates of around 6% for the age range of 5 to 11 years of age.[23] Higher prevalence figures reflect the number of children who fail a standardized test of motor coordination, rather than the number of children with severe coordination difficulties who have functional impairment in their activities of daily living (ADL) and/or academic achievement. Moreover, diagnostic tests should be found reliable and valid for use in the cultural setting of interest, otherwise inaccurate prevalence estimates might emerge as well. All studies agree that boys are affected more frequently than girls with an estimated 1.7 boys to 1 girl ratio.[1]

DSM-5[2] cites the following conditions as commonly occurring in combination with DCD:

- Problems of inattention, including attention deficit hyperactivity disorder (ADHD)
- Autism spectrum disorder (ASD)
- Speech and language disorders (SLD)
- Specific learning disabilities (especially reading and writing)
- Disruptive and emotional behavioural problems
- Joint hypermobility syndrome

DCD has increasingly been recognized as a significant co-occurring disability in children with other developmental disorders. Approximately 30% to 50% of children with ADHD are reported to show motor performance below age expectancy[39-41] and are severe enough to meet the criteria for DCD.[42] With regard to ASD, comorbidity figures of motor impairment range from 25% to 85%.[43-45] Motor problems co-occurring with SLD are recently estimated at 25% in children with developmental speech and language disorders and at 34% in children with scholastic disorders (i.e., a disability in reading or spelling together with a disability in mathematics).[45] These motor problems have a pervasive impact on children's performance in daily life or at school.[46] Developmental disorders appear relatively persistent as well, especially in case of co-occurring disabilities which increase the risk of long-term difficulties.[9, 12]

The varying grades of severity and symptoms, as well as comorbidity with other developmental disorders in children with DCD suggests various pathophysiological causes. Some children have a minor form of motor dyscoordination, whereas others have associated learning disabilities, attention deficit, and neurological soft signs (e.g., mild dysfunction in muscle tone regulation, choreiform dyskinesia, dysdiadochokinesis, difficulties with balance, fine manipulative disability, and difficulties in coordination between right and left limbs).

DCD is considered a multifactorial disorder in which both genetic and environmental factors such as perinatal adversity and inadequate physical activity play a role.[47, 48] Two population based twin studies estimated the heritability (comprising genetic and environmental effects) of DCD at .68[49] and .47.[50] The genetic component appears polygenic with many genes, all of small effect, thought to cause the disorder together or in interaction with unfavorable environmental circumstances.[51] In support of this a partially shared etiological background has been acknowledged between ADHD and DCD out of genetic and/or shared environmental factors. A significant familial correlation of .38 was demonstrated between motor performance measures and ADHD.[50] A twin study also reports an approximate heritability ranging from 29% to 51% between ADHD and DCD.[49] However, to date little is known about the specific genetics factors involved in DCD. A recent genome-wide association study investigated genes contributing to motor coordination problems in children with ADHD (n=890).[51] It was hypothesized that the presence of motor coordination problems in children with ADHD may identify a sample of reduced genetic heterogeneity.[51] Bioinformatics analysis exposed an augmentation of genes involved in motor neuropathy and Amyotrophic Lateral Sclerosis (ALS).[51] Genes involved in neurite (axons and dendrites) outgrowth and basic muscle function were also enriched. Among the highest ranked genes were *MAP2K5*, involved in Restless Legs Syndrome, and *CHD6*, causing motor coordination problems in mice.[52-54] In addition, a number of top-ranked SNPs or (single-nucleotide polymorphisms) were demonstrated to associate with Developmental Coordination Disorder Questionnaire (DCD-Q) subscales.[51] Replication studies are required to confirm and extend these initial findings on the genetics of DCD.

DCD, as currently defined, has also been described as minimal CP, putting DCD on the low end of the continuum of neuromotor disabilities.[55] CP is primarily a motor disorder and an umbrella term to describe a group of developmental disorders of movement and posture with an estimated prevalence of .1-.2% of live births. The motor impairment and consequent activity limitations are attributed to non-progressive disturbances in the developing fetal or infant brain'.[55] The main risk factor of CP is preterm birth, which has also been associated with increased positive screening of DCD.[56] It has been hypothesized that in some children with DCD, the neural substrate of DCD might mimic that of CP.[57] In support of this, neuroimaging data suggest that moderate to severe brain lesions, in particular those involving the WM, are associated with DCD in children with perinatal adversities.[58] WM abnormalities in sensorimotor pathways are the most common neural feature in children with CP as well and form the basis of their motor impairment.[59] However, according to a recent review,[57] available studies on this topic have small sample sizes and did not find a relation between MRI abnormalities and motor impairment. Consequently, no consensus has been reached on adding DCD to the CP category. A more complete clinical assessment including imaging, such as MRI, in addition to standardized clinical testing may provide a better understanding of DCD, and associated symptom-specific neural features.[60]

1.1.2 Impaired visual-motor skills in children with DCD

According to a meta-analysis,[61] difficulties in performing visual-motor tasks is a core symptom in children with DCD. Their motor performance is usually slower, more clumsy, less accurate, and more variable than that of their peers. Extensive behavioural studies denote impairment in the execution of fine motor tasks that require interaction of visual and motor systems, as for writing[62-65] and drawing.[66-69] Besides, difficulty with handwriting in children with DCD is one of the primary reason for referral to health care professionals.[70]

A substantial number of clinical tests assess graphomotor skills in children because of their sensitivity to neurodevelopmental delay and/or deficit. In addition, these test batteries are applied for diagnostic purposes, evaluating readiness for school and learning ability. An exemplary list of norm-referenced and valid test batteries of fine visual-motor skills in children include:

- Beery-Buktenica Developmental Test of Visual-Motor Integration - sixth edition (Beery VMI; Figure 1)[71]
- Bender Gestalt Test - second edition[72]
- Developmental Test of Visual Perception – third edition (DTVP-3 eye hand coordination and copying subtests)[73]
- Rey-Osterreith Complex Figure Test[74]
- SOS - second edition (a Dutch screening test to identify handwriting Impairments in children)[75]

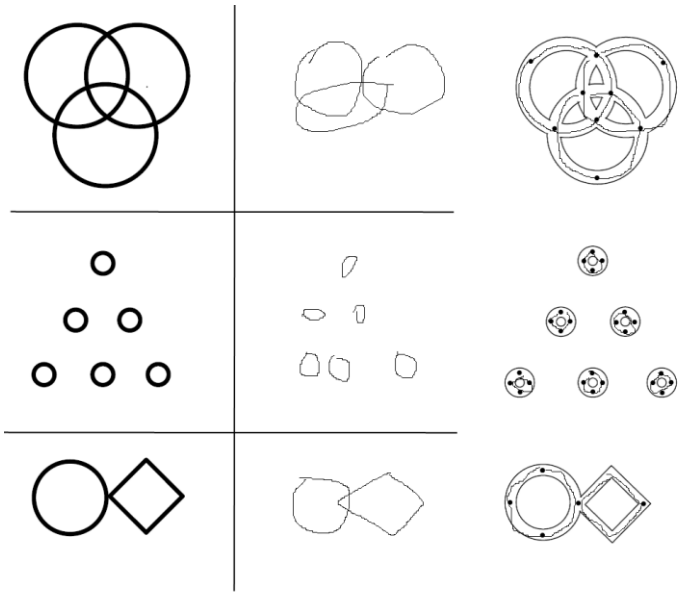


Figure 1. Exemplary Beery VMI items from the copy (left column) and trace subtests (right column). Erroneous copying performance is demonstrated (middle column) and figure line crossing denote tracing errors following the manual's scoring criteria.[71]

1.1.3 Underlying deficits of disordered visual-motor skills in DCD

Several deficits have been associated with impaired visual-motor skills in children diagnosed with DCD. These deficits comprise predictive control, motor timing, executive function, and sensoriperceptual functioning as confirmed by a recent meta-analysis and further explained below.[76]

Predictive motor control. Children with DCD have difficulties using predictive estimates for online correction of movements, causing increased errors in terms of speed and accuracy.[77-79] As a result, a child with DCD may be less able to train (or recalibrate) predictive models for action and movement skills, despite extensive practice. Deficient predictive control may affect visual and manual tracking,[67, 80-82] and catching abilities.[83-87] For instance, children with DCD were found less able to synchronize their eye movements to a moving target that followed a predictable sinusoidal path.[88] Greater temporal error suggested that the predictive model for the eye movement was less well refined, regardless of whether the tracking response was ahead or behind the target.

Rhythmic motor timing. Children with DCD generally display more variability in the ability to maintain a stable coordination pattern at a constant speed, spatially and temporally across unimanual and bimanual movements, as well as under different task modalities: auditory–motor, visual-motor synchronization, and self-paced responses.[89-92] Unlike in typically developing children, external pacing does not improve rhythmic performance in children with DCD. The pacing frequency also influences the type of temporal errors in DCD. Faster pacing frequencies cause temporal delays in children with DCD during unimanual movement.[93] Contrary, children with DCD are less able to slow down their tapping rate at slower frequencies in a bimanual auditory–motor coupling task.[91] Conceivably, greater inhibitory demands at lower movement frequencies also mediate timing deficits in children with DCD.[94, 95] Besides inhibitory functioning, predictive control is involved in efficiently mapping rhythmic responses to the required tempo.[91] In the case of externally cued action, for example, these learned perceptual–motor maps enable the child to synchronize movement to the visual or auditory cues by anticipating the dynamics of the limb and the timing of the stimulus.[91] This type of predictive control is affected in children with DCD.[76] Whether this underlying control deficit is explained by delayed development or deviance is not entirely clear. However, similar response delays area also present in younger typically developing children for both in-phase and antiphase movements, suggesting that they too do not have fully developed predictive control in synchronizing movements. Instead of using a predictive mode of control, they rely more on slower sensory feedback which requires higher processing demands.[96]

Executive functions. Pervasive difficulties have been noticed in executive functions (also known as cognitive control and supervisory attentional system)[97] in children with DCD, including working memory (visuospatial and verbal)[98, 99], inhibitory control,[94, 100] and executive attention.[95, 100] This confirms Piek et al.'s (2007)[101] suggestion of a generalized executive dysfunction as a common deficit in DCD. These executive deficits may especially interfere with motor tasks that entail high level processing as for example in fine motor activities.

Sensoriperceptual function. Significant evidence also designates deficits in the perception of sensory stimuli.[102] Visual processing deficits in children with DCD include basic visual form identification and motion detection which have consequences for planning visual-motor behavior.[61 103-106] These visual

processing issues in DCD may possibly initiate from magnocellular and parvocellular pathways, and their reciprocal connections to predictive and online control networks.[76] Below normal tactile perception has been reported in children with DCD for manual form matching and may complicate object manipulation in association with visual object information.[107, 108]

Taken together, performance deficits in DCD present across a range of tasks requiring visual-motor coordination. The reduced ability to learn these skills might be associated with a maturational delay or dysfunction, affecting neural connectivity associated with predictive control, motor timing, executive, and perceptual functions. Extensive neuroimaging research is required to clarify the underlying systems and neuropathology of these deficits. The next section introduces MRI methods that are used in neuroimaging research to capture the neural correlates associated with deficits underlying disordered visual-motor function relevant for DCD.

1.2 Magnetic resonance imaging

MRI has found widespread use in diagnosis of disease and basic brain research by visualizing soft tissue contrast of neurochemical and physiological mechanisms.[109] Both morphological and functional information is non-invasively investigated without using ionizing radiation as in computed tomography (CT) for instance. Moreover, MRI modalities have facilitated the study of neural features associated with specific motor and cognitive symptoms in developmental disorders.[110-112] This section describes the basic principles of structural MRI, functional MRI, and diffusion tensor imaging (DTI), as well as graph theoretical network analyses.[113] Untangling the brain structure and function of DCD-related motor disorders will result in a better understanding of their pathogenesis and ultimately more effective treatment for the individual child with DCD.

1.2.1 Structural MRI

Structural MRI applies the principle of nuclear magnetic resonance (NMR) in combination with magnetic field gradients for spatial localization. When hydrogen nuclei are placed in a magnetic field, a small fraction of the nuclei (i.e., protons) are magnetized preferentially along the direction of the magnetic field like small magnets. These spinning protons precess beside the magnetic field at a rotational rate (the Larmor frequency) that is typical in the radio frequency (RF) range (i.e., electromagnetic MRI pulse). This precession is analogous to that of a spinning top slowly rotating about the earth's gravitational field. A magnetic field rotating at the Larmor frequency excites the spins to a higher energy non-equilibrium state. Relaxation back to equilibrium evokes an energy emission which is the basis for the NMR signal (an 'echo'). MRI detects the spatial location of the signals using pulsed magnetic field gradients. These gradients cause the frequency of the spins to uniquely tie to their location within the magnet. By analyzing the frequency content of the echoes, the MRI is made.

The rate at which the magnetization returns to equilibrium is described with a time constant T1, and differences in this relaxation rate between different tissues such as gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) can be used to develop 'T1-weighted' contrast (Figure 2). Similarly, the rate at which the echo signal decays to zero has a time constant T2, also characteristic of tissue type, and 'T2-weighted' contrast can also be developed for tissue differentiation. Such images comprise the most commonly used forms of MRI contrast and provide the base for studies of neuroanatomical development. For example, fat tissue appears bright (high signal intensity) on T1-weighted images and relatively dark (low signal intensity) on T2-weighted images; water and fluids appear relatively dark on T1-weighted images and bright on T2-weighted images. T1-weighted images optimally visualize normal soft-tissue anatomy and fat (e.g., to confirm a fat-containing mass). T2-weighted images optimally show fluid and abnormalities (e.g., tumors, inflammation, trauma). Typically, a high-resolution MRI study of the whole brain anatomy includes the acquisition of a 3D volume of T1- and/or T2-weighted images.

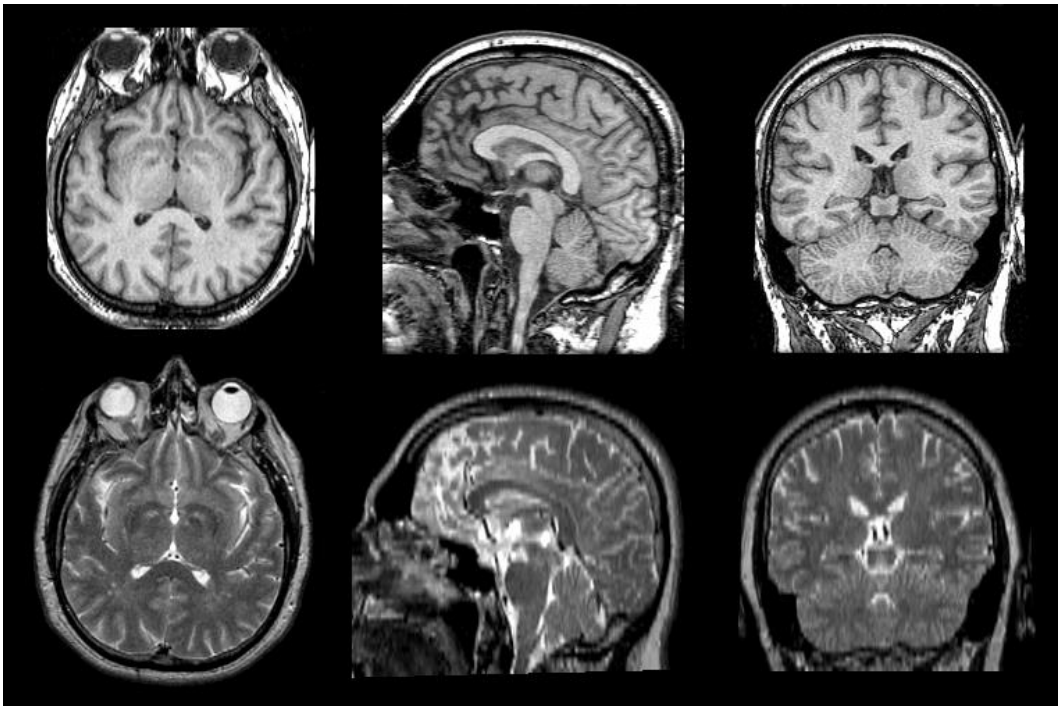


Figure 2. An example of T1 (top row) and T2-weighted (lower row) transaxial, sagittal, and coronal brain MR images.[114]

Substantial post-acquisition processing is necessary in order to assess structural differences between subject groups. The first step in post-processing often includes mapping the volume into a data structure with an isotropic resolution, using Fourier interpolation to preserve reliability. Second, segmentation is needed of the gray scale volume into GM, WM, and CSF (and sometimes others, such as tumor) tissue types by means of algorithms developed for this purpose. Some algorithms use a single-contrast data set, e.g., T1-weighted, while others depend on more than one contrast, such as both T1- and T2-weighted image volumes (multispectral approaches). A third step in image processing is to map the image volume into a common brain atlas such as the Talairach[115] or Montreal Neurological Institute (MNI) coordinates.[116] Finally, volumes of brain regions can be extracted and compared with those of a matched control group or normalized population means.

1.2.2 Diffusion tensor imaging

Diffusion tensor imaging (DTI) enables defining and quantifying anatomical links between brain regions through WM tracts. DTI is sensitive to the natural displacement of water molecules that occurs as part of the physical diffusion process. Water diffusion in biological tissue is however not uniform (isotropic diffusion) as it reflects interactions with obstacles, such as membranes, cytoskeleton and macromolecules (anisotropic diffusion). The diffusion patterns can there-fore indirectly reveal details about tissue architecture at a micrometer scale well beyond the usual millimetric resolution of MRI. DTI involves fitting a tensor, for each voxel, that estimates diffusion in

three dimensions.[117] The tensor is a mathematical description of an ellipsoid and the volume, shape and orientation of the ellipsoid can be considered. The length of the ellipsoid axes are represented by eigenvalues (λ_1, λ_2, λ_3), and respective orientations by means of eigenvectors (V1, V2, V3). Different quantitative indices can be derived from the estimated diffusion tensor; two primary DTI metrics are mean diffusivity (MD), reflecting the overall magnitude of water diffusion (mean of all three eigenvalues) and fractional anisotropy (FA), which indexes degree of directionality in water diffusion ranging from 0 when the diffusion is isotropic to 1 when diffusion occurs only along one axis (Figure 3). Additional DTI metrics include the estimated diffusion along [axial diffusivity (AD): λ_1] and across [radial diffusivity (RD): mean of λ_2 and λ_3] the main axis of the diffusion tensor. Another application is fiber tracking which maps the directional anisotropy of water diffusion, as visualized by bundles of fibers which can be used for fitting structural brain networks (cf. 1.2.3.) (Figure 4).

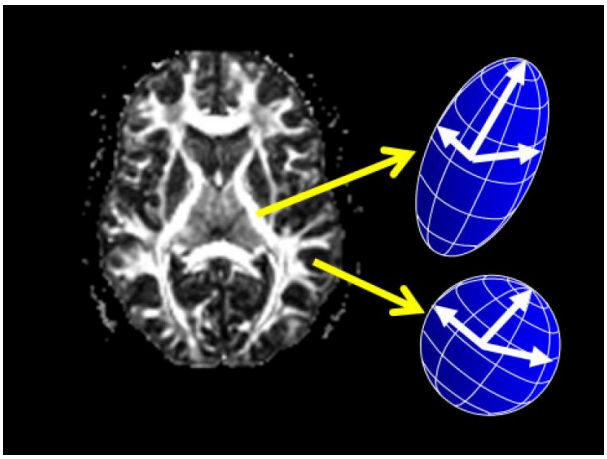


Figure 3. Axial FA map demonstrating the cylindrical 3D diffusion in white matter (due to geometrical fiber arrangement) opposed to grey matter with spherical diffusion.

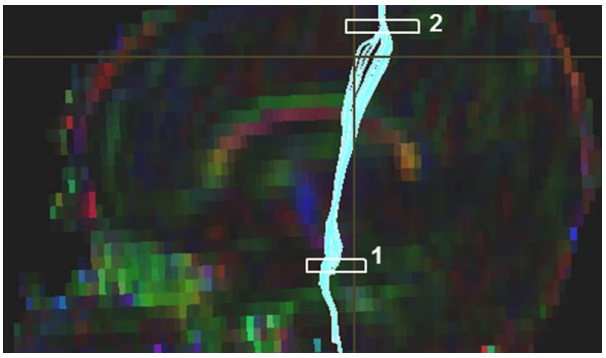


Figure 4. DTI tractography showing corticospinal tract (CST) fibers between cerebral peduncle (1) and precentral gyrus (2) regions in a preterm infant in the sagittal plane.[118]

The value of DTI in the assessment of neurodevelopmental disorders is that WM tracts of neurons constitute of myelin sheaths bundles that severely restrict the flow of water transverse to the axis of the bundles, while allowing relatively unconstrained diffusion of water along them. Consequently, the FA values in regions with intact WM bundles should be high because of the normally restricted diffusion pattern, whereas FA values are lower in regions where the bundles are disordered due to congenital or other defects that cause the removed or reduced restriction. FA maps can therefore be compared between different population groups to examine the presence of WM abnormalities (e.g., children with DCD vs. typically developing children). Therapeutic effects can also be evaluated by myelination increases as a potential biomarker within subject groups.

1.2.3 Network analyses

A complex network organization at different scales is considered in control of high level information processing of the human brain. The networks' topology allows efficient dynamic interactions between spatially distinct regions through oscillatory electromagnetic activities sustaining functionality. Specifically, the study of anatomical connectivity has highly benefited from the development of DTI based tractography (cf. 1.2.2).[117] Functional MRI has also offered the opportunity to quantify functional connectivity, as well as the so-called effective connectivity reflecting the causality or directionality among these signals (cf. 1.2.4).[119, 120] In conjunction with the development of advanced MRI methods studying brain network connectivity, the development of mathematical models using graph theory has modified the quantification and modelling of complex brain networks.[121-123] Graph theoretical analyses have been successfully applied on structural connectivity data from tractography DTI (cf. 1.2.2) refs, diffusion spectrum imaging (DSI),[124, 125] Q-ball imaging,[126] and cross-correlation of cortical thickness or volume.[127, 128]

To obtain graph theoretical analyses of DTI tractography data as employed in chapter 3, the cortex is firstly parcellated in regions corresponding to the nodes of the networks studied (Figure 5). Second, pairwise connections between nodes are defined in order to generate a connectivity matrix. This matrix is either binary (0 for an unlikely connection or 1 for a likely connection), resulting in an 'unweighted' graph or 'weighted' (i.e., representing the strength of the connection). Third, networks metrics can be calculated and compared to a random network with the same number of nodes and connections. The network's nodes and edges are represented by cortical regions, and connection as defined by a DTI tractography algorithm respectively. As no direction is available from tractography data, the graphs generated are undirected. From these graphs, network based metrics are typically derived to assert pathologies of the brain WM. An overview of commonly used metrics is given in Table 1.

Table 1. Definition of the commonest graph theoretical metrics used in structural and functional MRI studies

Clustering coefficient	The number of connections of a node with its nearest nodes (neighbours) proportionally to the maximum of possible connections in the network
Characteristic path length	The average number of minimum connections that should be passed to join any two nodes in the network
Global efficiency	Network efficiency to exchange the information at the global level
Local efficiency	Network efficiency to exchange the information at the clustering level
Degree	The number of connections of a node
Degree distribution	The probability that a randomly selected node has n connections in the network
Modularity	Network organization into modules or communities with high level of local clustering
Hierarchy	Measure how hubs are sparsely connected rather than provincially clustered
Centrality	The number of shortest paths between any two nodes that pass through this node and identify hubs
Small-worldness	How the network differs from a random network with the same number of nodes

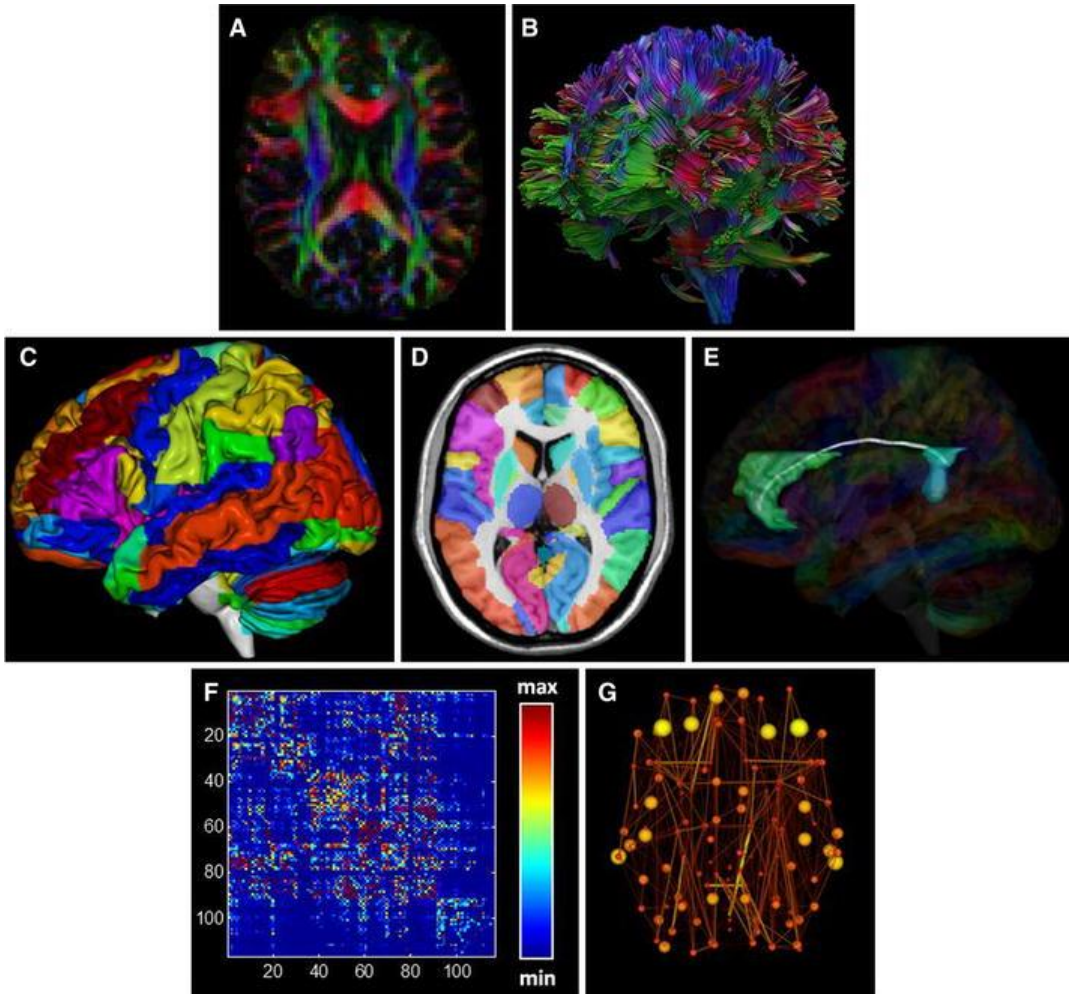


Figure 5. Flow chart for constructing a structural DTI-based network of an individual DTI dataset (A) using whole brain deterministic tractography (B). These color coded maps represent tracts running along the right-left, anterior-posterior, and superior-inferior direction in red, green, and blue. Tracts with an oblique angle are colored with a corresponding mixture color. A template e.g., the anatomical automatic labeling atlas (AAL),[116] consisting of 116 unique brain regions (C–D) segments the fiber bundles between each pair of regions of interest (ROIs). As an example, cortical regions and the WM fibers link the right anterior cingulate gyrus with the right posterior cingulate gyrus (E). The 116 × 116 matrix in F denotes the connectivity metric between each pair of AAL regions (e.g., the percentage of tracts). From the resulting brain network G, overall organizational characteristics and node-specific organizational characteristics are calculated. This figure is obtained from Caeyenberghs et al. (2014)[129(p199)] with permission.

Graph theory has provided a formal description of the complex brain network topology in vivo as well as a quantification of its properties. Such quantitative tools allow to better understand both pathophysiology and behavioural consequences (e.g., motor or cognitive symptoms) of brain-related disorders.

1.2.4 Functional MRI

The most common form of functional MRI relies on the MRI basics as described in 1.2.1, while also measuring regional hemodynamic responses over time in relation to stimuli presentation, task activation, or rest. Increased neuronal metabolism results in increased cerebral metabolic rate of oxygen and much greater increases in cerebral blood flow to the region; this uncoupling of oxygen consumption and supply during activation induces an excess of fully oxygenated red blood cells, which has a different magnetic state (diamagnetic) than in the non-activated state where the blood is more deoxygenated (paramagnetic). Hence, the hemoglobin acts as an endogenous contrast agent with an effect on the signal that depends on the local oxygen level, which in turn banks on local metabolism.[130, 131] The resulting blood oxygen level dependent (BOLD) contrast is by this means an indirect marker for neuronal activation, with temporal characteristics mediated by the hemodynamics. The BOLD contrast is usually no more than several percent in sensory tasks and is much smaller with tasks that require higher processing demands (e.g., motor control). For this reason, BOLD techniques do not allow for absolute tissue measure of perfusion, and only relative measures can be obtained. Therefore, activation experiments use designs in which there are multiple blocks or events that contrast both experimental and control conditions during a scanning session. The resulting activation maps designate the signal difference between the two averaged neuronal states (Figure 6). However, because of these small signal difference, statistical processing methods are employed to estimate activation. Such methods typically assume a linear model for the expected signal time series within one voxel as based on the task design and hemodynamics. A least-squares methods calculates the probability that the measured signal fits the model, i.e., the voxel is activated. A statistical correction for multiple comparisons (e.g., the false discovery rate method) optional to reduce the error of wrongly denoting voxels as significant (alpha error).

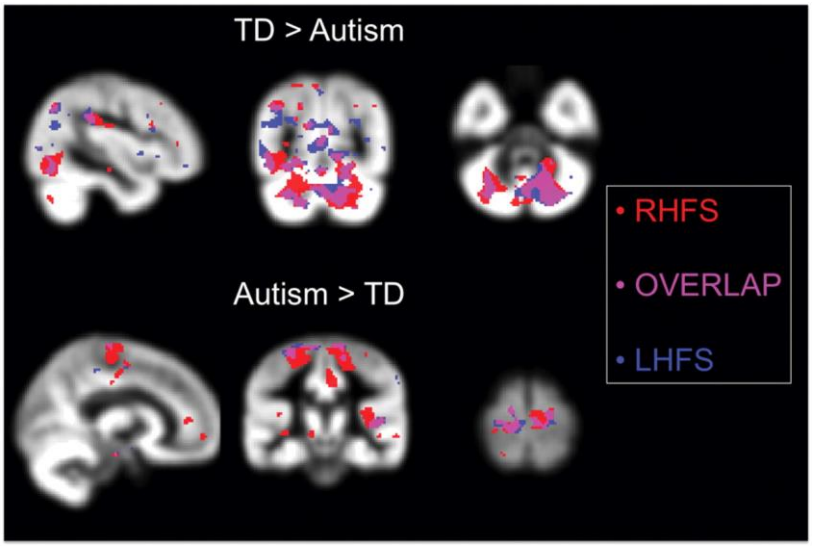


Figure 6. Demo of functional MRI maps denoting activation differences between children with autism and typically developing (TD) children during right-handed finger sequencing (RHFS), left-handed finger sequencing (LHFS), and the overlap between RHFS and LHFS from Mostofsky et al. (2009)[132(p2421)] with permission.

1.3 Neural correlates of developmental coordination disorder

The neuroscientific approach of studying DCD interprets the delayed or disordered motor skill developmen in terms of brain-behaviour interactions. A limited number of brain imaging studies have investigated group-level differences in brain structure and activation associated with motor or cognitive tasks between DCD and typically developing children.

1.3.1 DTI studies

Insufficient data is currently available on the contribution of WM alterations to motor behaviour in children with DCD. In a pilot study, children with (n = 7) and without DCD (n = 9 , aged 8 to 12 years), Zwicker et al. (2012)[133] used DTI to explore the integrity of motor, sensory and cerebellar WM tracts in the brain. Significantly lower MD of the posterior corticospinal tract and posterior thalamic radiation was obtained in children with DCD relative to controls. Lower AD significantly correlated with lower scores MABC-2[26] scores as a clinical test of motor abilities. This initial evidence suggests altered microstructural development of sensory and motor pathways children with DCD. Langevin et al. (2014)[134] assessed WM tracts that connect frontal and motor areas within the brain (corpus callosum, cingulum, and superior longitudinal fasciculus) using deterministic DTI based tractography in groups of children with DCD, ADHD, DCD+ADHD, and typically developing controls (n = 84; aged 8 to 17 years). Abnormalities unique to DCD were demonstrated in WM connections underlying the primary and somatosensory motor cortices as indicated by subtle decreases in FA for the left superior longitudinal fasciculus III. The DCD+ADHD group exhibited higher RD values in the anterior/superior frontal callosal region. This RD increase could reflect delayed or defective myelination.[135] Besides, FA was found significantly decreased in the DCD+ADHD and ADHD groups in the frontal region of the corpus callosum, which connects to prefrontal regions involved in cognitive control, executive functions, and attention.[136] From these findings, the motor and attentional problems in both ADHD and DCD seem to share a neurobiological basis in the corpus callosum, whereas these alterations are regionally and functionally distinct. The evidence of anomalous callosal development in motor and attention disorders was validated by correlations between diffusion measurements and participant performance on standardized tests of motor and attention/executive function performance, suggesting that structural changes affect behaviour. With respect to MD, RD, or AD, no changes were evident in any of the tracts studied for the single-diagnosis groups. This may be attributed to the use of full tract measurements which assume homogeneity and could therefore lack discriminative power to detect existing changes in anatomical subdivisions.[134]

1.3.2 Functional MRI studies

Activation patterns were measured in 7 children with DCD (aged 8 to 12 years) and 7 age- matched TD peers while performing a fine motor tracing task adapted from the Movement Assessment Battery for Children using a joystick.[137] Cerebellar between-groups activation differences were hypothesized from behavioural evidence of impaired predictive control, motor timing, and related neurological soft signs. Whole brain exploratory analysis revealed differing activation patterns in various brain regions. Significant differences were observed in the left inferior parietal lobule and right supramarginal gyrus (DCD > TD) and left inferior frontal gyrus and left precuneus (TD > DCD).

In addition, a small cluster of activity was found in the right cerebellar lobule VI that was significantly greater in the DCD than TD group. In a follow-up study,[138] using the same trail tracing task, brain activity was measured at baseline and after three days of practice outside the scanner. In this study, the DCD group displayed under-activation from the initial learning task to retention in the bilateral inferior parietal lobule (Brodmann area (BA) 40), right lingual gyrus (BA 18), right middle frontal gyrus (BA 9), left fusiform gyrus (BA 37), right cerebellar crus I, left cerebellar lobule VI, and left cerebellar lobule IX).

One more study examined visual-motor activity patterns in DCD during a visual-motor tracking task in which children followed an on-screen moving target with a joystick.[139] The DCD group demonstrated less posterior parietal activation in the DCD group; however, this result could be biased by a skewed results distribution due to one extreme outlier in the DCD group.[57]

Because of behavioural evidence of executive dysfunctions in DCD (cf. 1.1.3), Querne et al. (2008)[140] studied the attentional brain network in children with DCD and a control group using a go/no-go task in which participants responded when consecutive letters were presented (go) with the exception of "X" (no go). Using structural equation modeling to determine effective connectivity, the middle frontal and anterior cingulate cortex to inferior parietal cortex connectivity was increased in children with DCD. These results indicate less effective switching between go and no-go tasks in children with DCD and the need for additional recruitment of inhibitory brain responses to compensate.
Taken together, the understanding of neural mechanisms of DCD is improving with the use of advanced MRI techniques, although research is still in the early stages.[60] Current evidence suggests that WM abnormalities in sensorimotor circuits affect visual-motor performance in children with DCD.[57] These abnormalities may also trigger widespread compensatory functional activation patterns while performing visual-motor tasks as demonstrated with functional MRI.[3]

1.3.3 Neuropathology of visual-motor disorders

Visual motor disorders are one of the most consistent outcomes in follow-up studies of preterm children.[51, 141-143] As preterm birth is a known risk factor for DCD,[56] findings in preterm children may contribute to further research on the neuropathology of DCD. Deficient visual motor skills in this population have been attributed to a deficit in the dorsal visual stream, which is a neural network linking the occipital and posterior parietal cortices and its connections with prefrontal and premotor cortex, and hippocampal regions.[141, 142, 144] Basal ganglia injury sustained in the first 6 months of life independent of cortical lesions have also been shown to underlie altered visual development in children.[145] Besides this, models relating impaired development of brain networks to visual-motor deficits should include the cerebellum as well. According to a recent review, a growing body of evidence suggests a heightened risk for impaired cerebellar development in preterm children, even in the absence of identifiable perinatal cerebellar insults.[146] Reduced cerebellar volumes, moreover, seem associated with poorer visuospatial and visual-motor functioning in preterm children.[147] Afferent and efferent connections between the cerebellum and parietal regions also support involvement of the cerebellum in visuospatial and visual-motor functioning. However, further research is needed to understand these effects and their relation to the deficits in visuospatial and visual-motor functioning commonly observed in children with neurodevelopmental disorders.[146]

1.4 Aims and outlines

In spite of extensive behavioural studies, data on neural alterations related with DCD remains insufficient. However, the identification of neural features related with DCD is essential for more objective diagnostic procedures and treatment design. The main aim of this doctoral thesis is to extend initial findings on neural correlates of DCD-related visual-motor impairment which is a core symptom as outlined in this general introduction. The included studies focused on fine motor tasks that require interaction of visual and motor systems, as for writing[62-65] and drawing.[66-69] Moreover, these fine visual-motor difficulties in children with DCD are the primary reason for referral to healthcare professionals. This thesis presents novel MRI findings on brain structure and function as well as their implications for neurobehavioural functioning in children with DCD.

Chapter 1 provides introductory sections on DCD, MRI modalities and analyses as applied in the studies included in this thesis, as well as an overview of previous MRI findings in children with DCD.

The subsequent chapters correspond to individual manuscripts which are published (Chapters 2 and 4) and accepted for publication (Chapter 3). Therefore, a partial overlap between the chapters is possible as each manuscript is self-containing.

The developmental study in Chapter 2 investigated whether reaction time (RT) outcomes were predictive of visual-motor performance on clinical motor tests, including the Beery VMI in several age groups of typically developing children between 5 and 12 years of age. Those children's manual RT performance was investigated at predictively (regularly) and unpredictively (irregularly) paced stimuli by means of an experimental visual-motor reaction time (VRT) test. Deficient predictive motor control is considered a central performance deficit underlying visual-motor disorders in children with DCD. The Beery VMI and an adapted version of the VRT test have subsequently been applied in our DTI/structural network (chapter 3) and functional MRI study (chapter 4) respectively.

Chapter 3 encloses a study that evaluated the topological organization of the whole brain structural network and associated WM deficits in DCD. First, DTI was performed on data from children with DCD and typically developing controls: (1) reconstructing specific sensorimotor tracts along with the calculation of DTI measures (FA, RD, and AD), and (2) modeling structural brain networks using DTI fiber tractography, followed by state-of-the-art graph theoretical analyses. Secondly, associations were calculated between these DTI/network metrics and visual-motor deficits as measured with the Beery VMI to validate brain-behaviour relations. Finally, the ability of DTI/network data to discriminate between children with DCD and those with a typical development was investigated using stepwise discriminant function analysis.

Chapter 4 consists of a functional MRI study that investigated brain activation patterns from predictive and unpredictive RT performance in children with DCD and age- and gender-matched typically developing children. Aberrant neural activation was assessed for by contrasting predictive and unpredictive RT performance between both groups of children. In addition, processing speed as indicated by unpredictive RT was searched for its correlates with neural activation and again compared between groups for anomalies.

In the general discussion (Chapter 5), the main findings are summarized and put into perspective. On the basis of these findings, suggestions for future research and clinical implications and covering conclusions are made.

Chapter 2

Age-related differences in predictive response timing in children: Evidence from regularly relative to irregularly paced reaction time performance

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Human Movement Science (2012) August; 31

2 Age-related differences in predictive response timing in children: Evidence from regularly relative to irregularly paced reaction time performance

Abstract

Predictive timing refers to the anticipation and precise timing of planned motor responses. This study was performed to investigate children's predictive response timing abilities while accounting for confounding age-related effects of motor speed. Indices of predictive timing were evaluated for their contributions in motor skill proficiency as well. Eighty typically developing children in 4 age groups (5–6, 7–8, 9–10 and 11–12 years) performed a visual-motor reaction time (RT) test. Differences in speed and anticipatory responding at regularly relative to irregularly paced stimuli were evaluated as indices of predictive timing. Also, explicit timing and motor tests (M-ABC-2, VMI trace, and KTK jump) were administered. Significant faster responding for regularly vs. irregularly paced stimuli was found from the ages of 9–10 years on. Better anticipatory responding behaviour for regular in contrast with irregular stimuli was found to be present already at 7–8 years. Overall, predictive timing abilities increased across the 4 age groups. Also, inter-individual differences in the speed indices of predictive timing contributed to predicting VMI trace and KTK jump outcomes when controlling for age and overall motor response speed. In conclusion, predictive motor timing abilities increase during age 5 to 12 and correlate with motor skill performance.

2.1 Introduction

The development of motor skills involves a movement repertoire that can be flexibly tailored to different and specific task demands.[148] Typically, the acquisition of motor skills in children takes place through play and imitation. For instance, with repeated practice, children acquire accurate temporal predictions of motor actions (e.g., adopting a pace when running, rhythmic sequencing when typing or playing music). This learning of temporal sensorimotor information is necessary for adequate motor skill performance and thus might reflect one of the crucial processes underlying typical motor development.[149] The present study investigated age-related differences in predictive response timing in typically developing children.

Accurate predictive response timing is reflected in speeded and anticipatory motor behaviour due to temporal regularities in the occurrence of stimulus events. At regularly paced or rhythmic stimulus sequences, motor performance is considered to be predictive when RTs are faster relative to RTs at irregularly paced stimuli. In the latter case, RTs result from a passive feedback response mode.[150, 151] Although predictive timing received a great deal of interest from adult literature,[150-154] little is known about children's predictive response timing abilities.

When focusing on the development of children's simple RT performance, which is often used as a measure of response or processing speed, overall improvement (i.e., decrease) in RT performance throughout childhood is consistently reported.[155, 156] However, this age-related RT effect may also be determined in part by stimulus timing effects. Especially studies using a regularly paced task design may confound age-related changes in feedback based response effects with age-related changes in predictive response effects. To what extent children's RT performance at regularly paced stimuli benefits from temporal predictability and thus becomes predictive, is unclear. Other studies exclude all possible effects of predictive responding by using an irregularly paced RT task design.[156, 157] Consequently, knowledge on predictive response timing abilities in children is lacking in current developmental literature.

If predictive timing in children is age dependent, responding at temporally predictable events will result in speeding up effects in addition to general response speed effects across age. Indirect evidence for this hypothesis is drawn from developmental studies that investigated children's abilities to synchronize with rhythmic patterns.[156, 158] Synchronizing involves temporal encoding abilities that might not have been fully developed yet in young children. Synchronizing at isochronously (fixed) visual or auditory stimulus rates around 800 to 1500 ms is found to be sensitive in identifying age-related differences in child groups of 3 to 12 years of age.[158-161] In these studies, time differences between a child's response and the onset of the rhythmic pulse were calculated with shorter differences indicating better synchronizing.

In order to disentangle age-related RT effects adopted from a feedback based and predictive response mode, the present study compares RT performance respectively at irregularly and regularly paced visual stimuli. Since both interval types only differ in their temporal properties, predictive timing can be evaluated. To the best of our knowledge, this is the first developmental study using such design to study predictive response timing in an unconfounded way. Moreover, this kind of visual-motor reaction time (VRT) test involves simple stimulus-response mappings and visuospatial processing; children are thus expected to rapidly learn to respond. Different response

timing indices can be deduced from an analysis of resulting RT performances. RT reduction at regularly vs. irregularly paced stimuli can be used as a behavioural index of predictive timing abilities, i.e., the greater the RT decrease, the more predictive the RT performance.[150, 162] In addition, the occurrence of anticipatory responses, typically defined as RT beneath 100 ms,[163] indicates that they are planned and initiated in advance of target appearance. The ability to produce anticipated responses serves as an index of the precision of voluntary motor responses initiated in omission of external sensory guidance. Furthermore, increasing effects across different runs of the task (i.e., learning rates) can be evaluated. Because explicit knowledge of timing manipulations employed in this paradigm may also influence the motor behaviour of the child, the impact of explicit awareness is minimized by limiting deviance in random vs. regular time intervals. Furthermore, explicit awareness is assessed by evaluating possible effects of visual pacing differences in self-paced sequences and by asking the child whether she/he noticed any differences in stimulus timing during the visually paced RT task.

Although there is substantial evidence concerning the importance of motor timing abilities in diverse motor skills in children like drawing, balance and ball catching skills,[66, 164, 165] the exact nature of those mechanisms from the perspective of motor skill development has not been properly explored yet. Dynamic balance control is found to be associated with motor response speed in 11–13 year old children, suggesting the importance of feedback control in responding to destabilizing hip abductions-adductions.[164] To evaluate dynamic gross motor coordination and fine motor activity, respectively, the KTK sidewise jumping test[166] and the VMI trace test[4] were selected for this study. The KTK jump test involves rhythmic and smooth coordination between flexor and extensor leg muscles in a regularly paced sequence.[69] Given this rhythmic motor component, we expect indexed predictive response timing abilities to contribute in predicting children's KTK performance. VMI trace requires the child to perform feedback based, discontinuous movements, i.e., to start and stop drawing movements at the right time, in order to trace within the trail. For that reason, overall motor response effects are expected to predict VMI trace outcomes in children rather than indices of predictive timing.

In sum, the current study aimed to investigate children's predictive response timing abilities and assess age-related effects. To our knowledge no other developmental studies have attempted to behaviourally index predictive response timing while accounting for progress in overall response speed in children's RTs. Our indices of predictive response timing were evaluated on their contribution to interindividual differences in motor skill performance as well.

2.2 Methods

2.2.1 Participants

Eighty pupils (40 girls and 40 boys, all Caucasian) without diagnosed developmental motor or cognitive problems were randomly selected from two preschools and four primary schools in Flanders (Belgium). All children were tested on the Movement Assessment Battery for Children-2 (M-ABC-2).[26] The M-ABC-2 is a norm referenced motor test with eight items for assessing manual dexterity (three items), ball skills (two items) and balance (three items). Only children with a M-ABC-2 score higher than the 15th percentile were included. Among participating children, no motor problems or indications thereof were identified as none of the children's MABC-2 scores were below

the 15th percentile. Additional information on age group and motor performance level is provided in Table 1. Permission was granted by the schools' principals and teachers and informed consent was obtained from the parents or legal guardians.

Table 1: Age group information, and mean (M) and standard deviation (SD) of M-ABC-2 percentiles, VMI trace, KTK jump raw scores within each age group.

Group	Girls	Boys	Age (years)		MABC-2		VMI trace		KTK jump	
	n	n	M	SD	M	SD	M	SD	M	SD
5-6	10	10	5.45	.44	46.80	5.47	18.05	2.90	24.85	6.53
7-8	10	9	7.39	.63	60.94	5.62	21.79	3.03	36.58	11.43
9-10	11	9	9.48	.57	54.0 5	5.47	25.00	3.15	55.80	8.37
11-12	9	12	11.52	.65	49.81	5.34	26.43	2.77	63.10	5.88

2.2.2 Materials and procedure

Visual-motor reaction time test. Commercial research software (E-Prime 2.0, Psychology Software Tools, Inc.) with timing accuracy to the millisecond precision level, was used to run the test and collect the behavioural data. Stimuli were displayed on a 15.4-inch LED screen located approximately 60 cm in front of the participant.

Responses were recorded by means of a response pad (CEDRUS RB-830) with functional (push) buttons corresponding with the right or left index finger. Participants rested the index finger of their dominant hand on the corresponding button and a foam pad was put under their forearm for comfort. The visual-motor reaction time (VRT) test consisted of two conditions within a blocked design: a visually paced condition including either regularly or irregularly paced stimuli to assess response timing and a self paced condition as an explicit timing control test. During the visually paced conditions, participants pressed a button as fast as possible in response to the stimulus, a red blowfish cartoon (2.6 × 1.8 cm; 2.48° × 1.72° of visual angle) that was centrally presented for 70 ms against a white background. In a regular visual pacing block, 20 stimuli with fixed inter stimulus interval (ISI) of 1200 ms were presented whereas in an irregular visual pacing block stimuli were presented, with random ISIs (900–1050–1200–1350–1500 ms). RTs and the number of anticipatory responses (RT < 100 ms) at the visually paced stimuli were registered. The average pacing rate is identical in both visually paced blocks i.e., one stimulus every 1200 ms. Predictive timing was indexed by the mean RT decrease (ΔRT M) and increased anticipatory responses (ΔAR% M) at regularly as opposed to irregularly paced stimuli. Higher positive scores for both indices indicate better predictive timing abilities. Mean RT at unpredictive stimuli indexed response speed (RT M irregular) with lower RTs indicating faster processing. Intra-class correlations demonstrated substantial test-retest reliability for each of the VRT outcome measures across successive runs: .85 (RT M irregular), .68 (ΔRT M), .and .72 (ΔAR% M) in the total group.

In the self paced condition, participants were instructed to reproduce the pacing of the preceding block by repeatedly pressing the response button for a period of 25.4 s (i.e., block duration of the visually paced blocks). As visual feedback, the blowfish stimulus was displayed in response to every button press. Inter response times (inter RTs) were registered, i.e., the time in between successive responses. The experiment comprised six runs in total. One run consisted of three blocks, including

one of each condition (regular pacing, irregular pacing and self pacing). The two visual pacing blocks always preceded the self pacing block and were counterbalanced across runs and in between subjects. Between blocks, a countdown timer indicated a 4 s pause. A self pacing block was initiated by the appearance of a music note symbol (1.7 × 2.1 cm; 1.62° × 2.01°) for 1 s and a visually paced block (regular or irregular) by the appearance of an eye symbol (2.5 × 1.4 cm; 2.38° × 1.34°) (Figure 1).

Jump item of the Körper Koördination Test für Kinder (KTK). The KTK[166] is a norm referenced test for gross motor coordination. The KTK jump item of this test consists of two 15 s trials in which side to side jumps over a low beam were performed, as many as possible while keeping both feet together. For scoring, the total number of correct jumps over both trials was used. The reliability of this KTK item is good with a test–retest correlation coefficient of .95.[166]

Motor Coordination' test of the Beery VMI trace test. The Beery-Buktenica Developmental Test of Visual Motor Integration (Beery VMI)[4] is a well-established normative test measuring the ability to copy geometric figures. In the supplemental test of Motor Coordination, the child traces 27 geometric forms with a pencil, without leaving the double-lined paths within a time frame of five minutes. For scoring the total number of correctly traced forms is used. This item will be referred to as the 'VMI Trace test' with an interscorer reliability of .93 and a test–retest reliability of .86.[4]

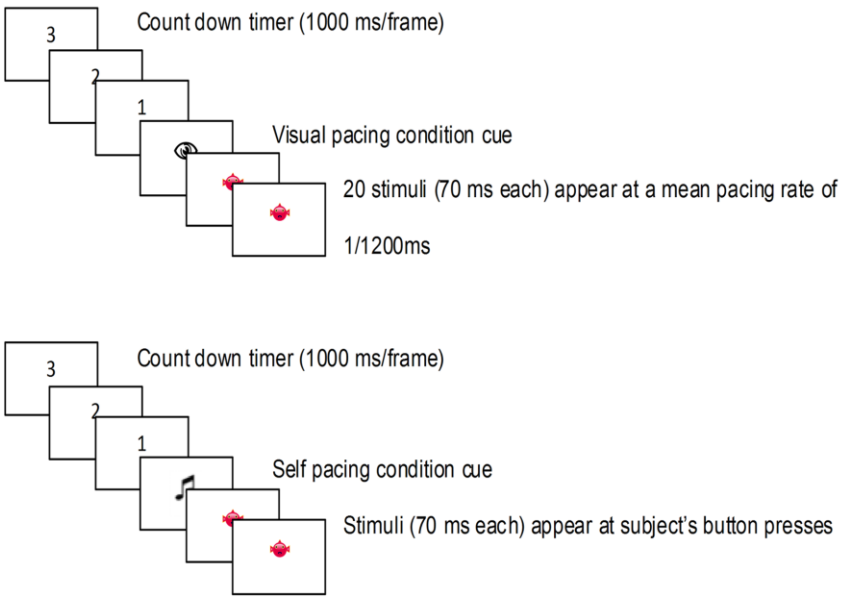

Figure 1. Schematic representation of the implicit timing task, visually paced (top) and self paced conditions (bottom).

Procedure. All procedures were approved by the ethical commission of Ghent University. Children were tested separately and began with a short practice session (20 trials) of the visually paced RT condition with feedback on RT and accuracy (number of responses within ISI) for comprehension and familiarization with task demands. The visually paced RT task was instructed to the child as 'a fish catching task' with the preceding eye symbol hinting preparation for the appearing fishes to catch by pressing the response button as fast as possible. A music-note symbol signified self pacing or so called 'tempo task' in which participants attempted to imitate/simulate the pacing of the previously appearing fish cartoon by pressing a button. After the experiment, children were asked whether they had been aware of any temporal differences during the visual pacing conditions. Next, they were told about regular and irregular pacing blocks in the fish catching task and asked again if they had noticed this. Subsequently, children were evaluated with the M-ABC-2,[26] the Motor Coordination of the Beery-Buktenica Developmental Test of Visual-Motor Integration – Trace test,[4] and the jump item of the KTK.[166]

2.3 Results

2.3.1 Visual-motor timing

The performance of the visually paced RT condition resulted in anticipatory responses (AR; RT < 100 ms), visually guided responses and missed responses. No significant age group differences were found on the number of missed responses within regular and irregular pacing stimuli blocks. For further RT analyses, missed responses were excluded.

2.3.2 Response speed

A repeated measures ANOVA (analysis of variance) to examine effects of age group (4 levels), condition (2 levels: regular and irregular pacing) and run (6 levels) revealed a main effect of age, $F(3, 76) = 46.503$, $p < .0001$, designating general faster responding with increasing age (Figure 2). Also the condition, $F(1, 78) = 34.847$, $p < .0001$, and Condition × Age interaction, $F(3, 76) = 11.553$, $p < .0001$, were significant, signifying differences in RT mean (M) between both pacing conditions which differed across ages. No other effects reached any significance. The Condition × Age interaction was further analyzed by testing the condition effect within age groups. At 5–6 years, no significant difference occurred between RTs at regular (M = 490 ms) and irregular (M = 491 ms) visual pacing, $t(1,19) = -.061$, $p = .952$. Subsequent age groups showed increasingly greater RT differences (7–8 years; regular: M = 374 ms, irregular: M = 377 ms, $t(1,18) = -.126$, $p = .901$, 9–10 years; regular: M = 284 ms, irregular: M = 340 ms [$t(1,19) = -5.488$, $p < .0001$] and 11–12 years; regular: M = 223 ms, irregular: M = 297 ms, $t(1,20) = -5.456$, $p < .0001$). Regression analysis to describe the Condition × Age interaction showed significant linear, $F(1, 78) = 30.170$, $p < .0001$, as well as quadratic functions, $F(2,77) = 15.271$, $p < .0001$, indicating that RT M differences (i.e., speeding in RT at regular relative to irregular pacing) increased with age and starts leveling off before the ages of 11–12 years.

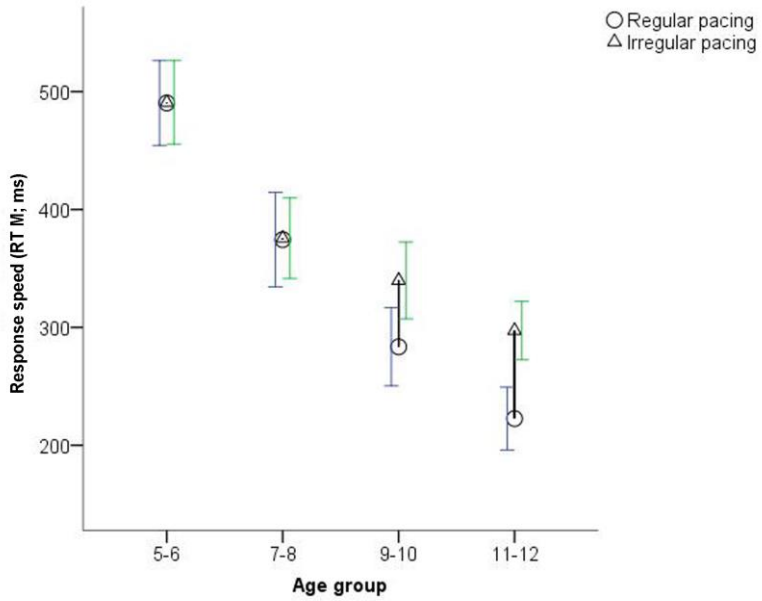

Figure 2. Response speed (RT Mean; ms) at regularly and irregularly paced stimuli averaged across runs in children of different age groups. Error bars represent 95% confidence intervals.

2.3.3 Anticipatory responses

A 4 (Age Group) × 2 (Condition: regular and irregular pacing) × 6 (Runs) repeated measures ANOVA on the percentage of anticipatory responses revealed a main effect of age, $F(3, 76) = 8.198$, $p < .0001$, reflecting more AR with increasing age (Figure 3). A main effect of condition, $F(1, 78) = 51.588$, $p < .0001$, and also the Condition × Age interaction, $F(3, 76) = 10.978$, $p < .0001$, were significant, indicating differences in AR between regular and irregular pacing conditions which differed between age groups. No other effects reached significance. To test at what ages a condition effect was manifest, within age group analysis showed that anticipatory responding at visual pacing already occurred at 7–8 years (regular: M = 7.18%, irregular: M = 4.04%) [$t(1, 18) = 2.856$, $p < .05$]) and likewise for the subsequent age groups of 9–10 (regular: M = 8.56%, irregular: M = 3.39% [$t(1, 19) = 3.526$, $p < .01$]) and 11–12 (regular: M = 18.34% and irregular: M = 6.61% [$t(1, 20) = 5.745$, $p < .0001$]), whereas the youngest age group did not show a condition effect (5–6 years; regular: M = 4.87% and irregular: M = 4.14% [$t(1, 19) = 1.025$, $p = 318$]). Regression analysis denoted both significant linear [$F(1, 78) = 30.010$, $p < .0001$] as well as quadratic [$F(2, 77) = 16.279$, $p < .0001$] functions describing a progressive increase of AR with age.

2.3.4 Explicit visual-motor timing

Inter RT (i.e., time between subsequent responses) M in the self paced condition was examined using a repeated measures ANOVA to test effects of age (4 levels), run (6 levels) and preceding visual pacing condition (regular, irregular). This analysis did not show a significant main effect of the

preceding visual pacing condition, F(1, 78) = .037, p = .847, or Condition × Age interaction, F(3, 76) = .331, p = .803. Other effects involving run were not significant either.

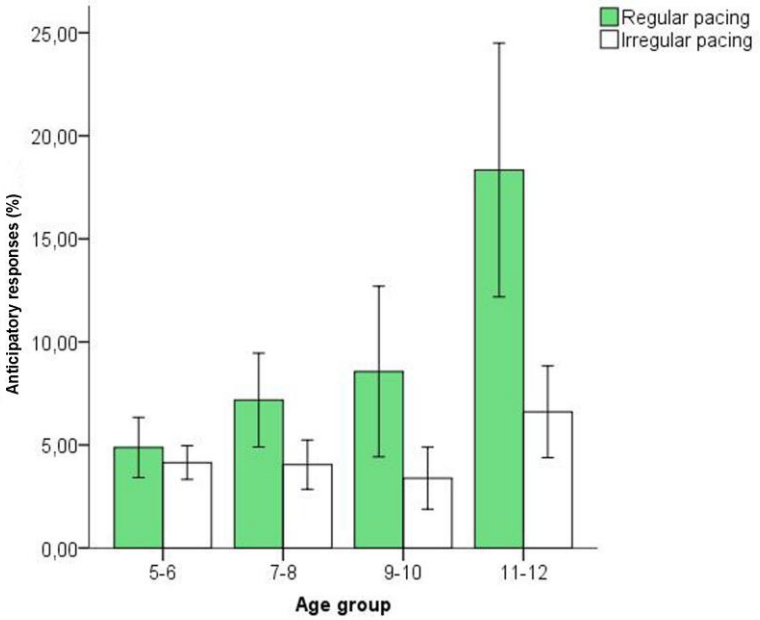

Figure 3. Percentage (%) anticipatory responses at regularly and irregularly paced stimuli averaged across runs in children of different age categories. Error bars represent 95% confidence intervals.

2.3.5 Predictive models for individual motor skill performance

Stepwise multiple linear regression analyses assessed which response timing indices in addition to age to enter in a regression equation for predicting motor skill performance. Two indices of predictive timing were calculated as follows: Difference scores of RT M at irregularly and regularly paced stimuli resulted in the respective index ΔRT M and differences in percentage (%) AR at regularly vs. irregularly paced stimuli resulted in the index ΔAR% with scores >0 indicating predictive timing. RT M at irregular stimulus pacing was also entered as an index of response speed. The initial model included predictive timing indices (ΔRT M, ΔAR%), motor response speed (RT M irregular) and age group as predictor variables and KTK jump and VMI trace scores as dependent variables. Predictors were eliminated from the model with a backwards selection procedure to achieve at the most sparing model. The resulting models consisted of ΔRT M and RT M irregular as significant predictors contributing unique variance to the KTK jump as well as VMI trace performance, even when controlling for age (Table 2). The model for predicting KTK jump scores, $F(3, 76) = 97.895$, $p < .0001$, explained 79% of the variance and the VMI trace model, $F(3, 77) = 45.550$, $p < .0001$, explained 64% of the variance.

Table 2. The unstandardized (B) with standard error (SE) and standardized regression coefficients (β) in the predictive models for motor performance of VMI trace and KTK jump scores.

	VMI trace			KTK jump		
	B	SE B	β	B	SE B	β
Age group	.56	.23	.29*	4.88	.68	.64**
ΔRT M	.02	.01	.30*	.06	.02	.20*
RT M irregular	−.02	.01	−.41**	−.03	.01	−.18*

* $p < .05$.
** $p < .0001$.

2.4 Discussion

This study was performed to investigate predictive timing abilities in children's simple visual RT performance. Differences in speed and anticipatory responding at regularly relative to irregularly paced visual stimuli were evaluated as indices of predictive timing. Overall, predictive response timing abilities were found to increase during the ages of 5 to 12 years. Significantly faster responding for the regularly vs. irregularly paced stimuli was found from the ages of 9 to 10 years on. Better anticipatory responding behaviour (i.e., voluntary motor responses initiated in omission of external sensory guidance) was already present at the ages of 7 to 8 years. With consecutive runs of the task, 5- and 6- year- old children did not exhibit predictive responses at an average pacing rate of 1200 ms. Their RT at regularly and irregularly paced stimuli was not significantly different which indicates a merely passive feedback based response mode instead of active anticipation of the next stimulus. These results add to the current developmental literature on synchronizing skills in children as our study induced synchronizing-like behaviour in speeded responding at regularly paced stimuli. Less fine-tuned synchronizing noted in this youngest age group in, e.g., Sasaki (1997),[161] seems to involve a failure to perform predictive responses. Our data do not comprise information on possible extra responses within one ISI, so-called disinhibitory responses because only the first response within one ISI was registered. Although younger children's responses are slower and disinhibitory responses might have occurred, these overall response effects could not have confounded our results since RT statistics were used at regularly relative to irregularly paced stimuli. Previous studies estimated a preferred pacing rate at around 500 ms based on spontaneous self pacing rates in children aged 3 to 12 years.[160, 161] Given the evidence of a preferred pacing rate, perhaps a degree of predictive responding is inducible also in 5- to 6- year- old children when using 500 ms pacing rates in an analogous task design. Also, we cannot exclude that training across different test sessions or longer pacing blocks might result in improved predictive response timing across age groups.

Concerning motor skill development, children's speed index of predictive timing as well as motor response speed (i.e., feedback based RT performance at irregularly paced stimuli) significantly contributed to the prediction of performance outcomes on a sidewise jump task, even when controlling for age. Sidewise jumping to and fro entails a definite rhythmic component and henceforth the expected contribution of predictive response timing was confirmed. The additional significant correlation of feedback based motor response speed is not surprising. Precise feedback based response abilities are a necessary prerequisite to perform subsequent predictive responding. Predictive response timing uses feedback information from previous reactive responses: the timing

between movements (inter response interval) as well as information on the timing error (response latency).[167] Unlike sidewise jumping, tracing does not involve rhythmic movements and therefore hypothesized to entail less predictive timing requirements. Tracing implicates the child to perform feedback based movements, i.e., to start and stop drawing movements at the right time. Accordingly, our data denoted a substantial correlation with feedback based motor response speed relative to predictive timing and age effects. The differential contributions of predictive timing abilities as indicated with differences in beta regression coefficients are in line with VMI tracing and KTK sidewise jumping that clearly differ in their temporal requirements.

Several runs of the task were administered in order to investigate possible learning effects in predictive response timing abilities within one test session. In agreement with findings in adult samples, no evidence was found of any learning effect across runs.[154] Apparently, a fast learning effect of predictive responding is present in children within the first run, which is maintained throughout the task in children of 7 years on. Because motor tasks often differ in temporal as well as action sequencing demands, the underlying accounting processes in developing motor skills are not well distinguished yet. By reducing action sequencing and explicit demands, the simplicity of this predictive response timing task may place less demand on prefrontally mediated skills, such as maintaining an action sequence or temporal pattern in working memory during the learning process. As a result, this task can easily be evaluated and trained in young children.

The improvement in RT performance gained from a predictable, temporally regular task structure has been assigned to optimized motor processing,[168] but may also be mediated by premotoric stages of processing, such as response selection[169] or sensorimotor association.[167] Evidence from typically developing adult samples suggests that predictive timing in motor responding is regulated by internal chronometric, neural timekeeping systems that entail well-defined frontostriatal and frontocerebellar circuits.[153] Maturational changes in the brain have been demonstrated to coincide with motor developmental progress. Structural as well as functional age-related changes of striatal and cerebellar systems have been shown in pediatric neuroimaging and motivate further investigation of possible neurodevelopmental changes underlying predictive response timing processes.[170, 171] Possibly neural development during childhood underlies the use of adaptive strategies to enable predictive response timing.

2.4.1 Future Directions and conclusions

Predictive control is thought to progressively improve over childhood. Therefore, it would be instructive to extend the age range of the group to cover adolescent development. We also know little about within-child stability; for instance, to what degree performance among children varies as a function of age relative to specific maturational and/or environmental factors. Hence, longitudinal data is necessary to evaluate these developmental characteristics. Also, we believe that the use of functional neuroimaging techniques like functional MRI will enable to entangle the neural networks underlying predictive response timing in children.

Overall, this study extends our understanding of how predictive responding develops with age. Results from the visual-motor RT test show clear age differences over the age range studied, with significant improvements occurring after 7 to 8 years of age. These changes are consistent with those found for predictive control.[172] The reduced ability of the youngest group (5 to 6 year olds) to

perform predictive responses, therefore, reflects their inability of an adaptive motor performance. This was further illustrated by our findings of significant predictive models of jumping and tracing performance that included individual predictive RT outcomes. The continued refinement of predictive control over young and middle age childhood holds important implications for skill development in typically developing children and in those with developmental motor disorders such as Developmental Coordination Disorder (DCD). Therefore we hypothesize that the maturation of neural systems supportive of predictive control may serve as a powerful predictor for skill proficiency development in children. Performing adaptive and synchronized movements relies on the ability to predict movement dynamics which emerges from ones physical movement and perceptual sensations. As such, the development of predictive control reduces the child's reliance on slower feedback control, which is beneficial for automatization of actions.

2.5 Acknowledgments

The authors are thankful to all the teachers and children for their participation in this study. They also wish to thank Ellen Deschepper for statistical advice.

Chapter 3

Brain connectomics of visual-motor deficits in children with developmental coordination disorder

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3 Brain connectomics of visual-motor deficits in children with developmental coordination disorder

Abstract

Developmental coordination disorder (DCD) is a neuromotor developmental disorder in which visual-motor deficiencies significantly affect a child's daily activities. The primary study objective was to extend preliminary findings on specific white matter deficits in DCD and structural connectivity in children with DCD. Diffusion magnetic resonance imaging (MRI) based tractography was used to identify abnormal microstructural properties of specific sensorimotor white matter tracts in 21 children with DCD between 8 and 10 years and 20 age-gender matched typically developing (TD) controls. Graph theoretical analyses were applied to evaluate whole brain connectomics. Associations were also calculated between the tractography/connectome results and visual-motor performance, as measured with the Beery-Buktenica Developmental Test of Visual Motor Integration. Significant positive correlations were obtained between visual-motor trace scores and fractional anisotropy (FA) in the retrolenticular limb of the internal capsule within the DCD group. Moreover, lower FA in sensorimotor tracts and altered structural connectivity were observed for the DCD children. Compared with controls, subjects with DCD showed decreases in clustering coefficient, global and local efficiency, suggesting a weaker structural network segregation and integration. The degree of decreased global efficiency was significantly related with poor visual-motor tracing outcomes, besides FA reductions. Specifically, nodal efficiency at the cerebellar lobule VI and right parietal superior gyrus were found significant predictors to discriminate between DCD and TD children. Specific white matter alterations and network topology features associate with visual-motor deficits and the DCD diagnosis, indicating the clinical potential of diffusion MRI based metrics for diagnosing DCD.

3.1 Introduction

Developmental coordination disorder (DCD) is a neuromotor developmental disorder that significantly interferes with a child's ability to perform daily activities that require adequate visual-motor skills, such as writing, playing computer games and sportive skills.[2] DCD impacting quality of life and well-being has a prevalence of approximately 1.8%. High phenotypic variation is found in DCD-related motor problems in terms of severity and disposition.[1] Moreover, DCD is often diagnosed together with other developmental disorders such as attention deficit hyperactivity disorder (ADHD), autism spectrum disorder or dyslexia.[3, 173] Due to this heterogeneous clinical presentation, uncertainty exists regarding diagnosis, prognosis and pathogenesis of DCD. Although neuroimaging research on DCD has extended in recent years, the neuropathology of DCD remains poorly understood and is hence lacking diagnostic markers.[3]

For research purposes, brain connectivity has been investigated in DCD, most commonly using functional MRI and diffusion tensor imaging (DTI).[133, 134, 137-140, 174] Functional MRI studies have demonstrated widespread and task-specific activation differences coinciding with DCD-related sensorimotor, as well as cognitive performance difficulties.[3, 175] Atypical activation during fine visual-motor performance is thought to reflect compensatory strategies,[68, 138] which may result from aberrant structural properties of brain white matter (WM). However, insufficient data is available on the influence of structural WM alterations to visual-motor impairment in children with DCD according to recent reviews.[57, 175] In a pilot study of children with (n = 7) and without DCD (n = 9 , aged 8 to 12 years), Zwicker et al.[133] used DTI to explore the integrity of motor, sensory and cerebellar WM tracts in the brain. Significantly lower mean diffusivity (MD) of the posterior corticospinal tract and posterior thalamic radiation was observed in children with DCD relative to typically developing (TD) controls. Lower axial diffusivity (AD) significantly correlated with lower scores on the MABC-2[26] scores, which is a clinical test of general motor abilities. Another study of Langevin et al.[134] focussed on WM tracts that connect frontal and motor areas (i.e., corpus callosum, cingulum, and superior longitudinal fasciculus) using DTI tractography in a group of children with DCD, ADHD, DCD+ADHD, and TD controls (n = 84; aged 8 to 17 years). DCD-related abnormalities could be demonstrated in WM connections underlying the primary and somatosensory motor cortices as indicated by subtle decreases in fractional anisotropy (FA) for the left superior longitudinal fasciculus III. This evidence suggests altered microstructural development of sensory and motor pathways children with DCD.

Alternatively, network-based metrics of structural connectivity can be more sensitive to alterations that are less apparent in gross structure (i.e., WM integrity) because they consider each region's integration into the global unit rather than as an independent entity.
This study aimed using fiber tractography combined with a graph theoretical approach to investigate the structural organization of the WM networks in a DCD group without other diagnosed developmental disorders and TD children. Structural connectivity decreases in the DCD vs. TD group were expected to manifest in (1) specific diffusion MRI metrics of sensorimotor pathways (i.e., the corticospinal tract and posterior thalamic radiation) relying on the previous Zwicker et al.'s study,[133] (2) graph theoretical network metrics assessing overall structural connectomics. Moreover, we hypothesized that these decreases in structural connectivity would correlate with deficits of visual-motor performance as measured with the Beery-Buktenica Developmental Test of Visual Motor Integration (Beery VMI).[4] This study focused on the Beery VMI as this test is (1) widely used in clinical

facilities to diagnose graphomotor deficits,[62] (2) a prototype of complex sensorimotor integration, requiring visuospatial inputs into a mapped motor responses, and (3) well-validated with sound reliability scores. Finally, we examined whether diffusion MRI and network parameters can provide diagnostic information that is complementary to behavioural assessment.

3.2 Methods

3.2.1 Subjects

All 8-to 10-year-old children were recruited using institutional ethics commission approved advertisements placed in schools and ambulant rehabilitation centers. For inclusion, children had to be otherwise healthy, with no history of psychiatric or developmental disorders other than DCD. In addition to integrating the information received from motor assessments and parent interviews, a critical role of the paediatrician was to perform a physical and neurological examination to rule out other possible causes of motor incoordination.

3.2.2 Standard protocol approvals and patient consent

Study permission was obtained from the ethics commission of Ghent University. Written informed consent was acquired from legal guardians and child assent before testing.

3.2.3 Clinical diagnostic assessments of children with DCD and TD children

Diagnoses of DCD and typical development were supported by direct interview of the child and parents together using a clinical questionnaire (parent version of the MABC-2 checklist), and assessment of the Movement Assessment Battery for Children-second edition (MABC-2).[26] The MABC–2 is evaluates children's performance of manual dexterity, ball skills, and balance and is validated for DCD screening.[26] Test-retest reliability for the total score was excellent, with an intra-class correlation coefficient of .97 and internal consistency of .90 with Crohnbach's alpha.[176] Children with DCD were only included if their MABC-2 performance was at or below the 5th percentile, indicating motor coordination difficulties.[2] TD children were excluded from participation if their total MABC-2 score was below the 16th percentile (borderline motor problems). DCD symptom presence in activities of daily living was confirmed using the MABC-2 checklist. Children with other diagnoses, e.g., ADHD, autism spectrum disorder, conduct or mood disorders, were excluded. All children had to obtain an estimated total intelligence quotient (TIQ) of ≥ 85 to ensure the exclusion of children with intellectual disabilities. The short form of the Wechsler Intelligence Scale for Children-third edition (WISC-III, Dutch version)[177] was used to estimate the child's TIQ, verbal IQ (VIQ), performance IQ (PIQ). The WISC-III short form have an estimated reliability and validity of .92 and .93 respectively.[177] TIQ was calculated using averaged standardized scores of the block design, picture arrangement, word similarities, and comprehension subtests. PIQ and VIQ resulted from averaging standardized scores on the performance (block design and picture arrangement) and verbal intelligence subtests (word similarities and comprehension) respectively.

3.2.4 Visual-motor skill assessments

Visual-motor skills were assessed comprehensively using the Beery-Buktenica Developmental Test of Visual Motor Integration (Beery VMI) – 5th edition which is a valid clinical test battery with age-norm references.[4]
The Beery VMI requires the integration of visual perception into eye-hand coordination for completing the copying (VMI copy) and tracing (VMI trace) of a sequence of geometric figures using a pencil on paper forms. A motor-free control test involving visual discrimination of the geometric figures was also administered (VMI visual discrimination).

3.2.5 MRI and diffusion tensor MRI data

Standard protocols were used for high-resolution T1, and DTI to assess WM disruption. MRI examination took place without sedation on a 3T Siemens Magnetom Trio MRI scanner system (Siemens Medical Systems, Erlangen, Germany) with an eight channel phased-array head coil. A diffusion weighted single shot spin-echo echoplanar imaging was acquired with data acquisition matrix = 96 × 96; field of view = 190 × 190 mm^2; repetition time = 9900 ms, echo time = 102 ms, and 60 contiguous sagittal slices (slice thickness= 2.0 mm; voxel size = 2.0 × 2.0 × 2.0 mm^3) covering the entire brain.[178] Diffusion gradients were applied along 30 non-collinear directions with a *b*-value of 1400 s/mm^2. Additionally, one set of images with no diffusion weighting b = 0 s/mm^2 was acquired. Moreover, for all subjects, high-resolution T1-weighted structural images were collected in the sagittal plane [176 slices with parameters: repetition time = 1550 ms, echo time = 2.39 ms, image acquisition matrix = 256 × 256, field of view = 220 × 220 mm^2, flip angle = 9°, slice thickness = 0.9 mm, distance factor = 50%, voxel size = 0.9 × 0.9 × 0.9 mm^3 (resized to 1 × 1 × 1 mm^3)].

DTI data were analyzed and processed in ExploreDTI,[179] as previously described.[180, 181] The DTI processing consisted of (a) Subject motion and eddy-current induced geometrical distortions correction[182] and (b) diffusion tensor estimation using a non-linear regression procedure.[183] Fractional anisotropy (FA), radial diffusivity (RD), and axial diffusivity (AD) were calculated in a selected set of afferent and efferent pathways, considered important for visual motor integration and eye-hand coordination.[184] These sensory and motor regions of interest (ROIs) were reconstructed and depicted on FA of the Mori et al. (2005)[185] atlas. (Figure 1).

3.2.6 Network construction and graph analyses

Brain networks were reconstructed using identical procedures as in previous studies.[186, 187] (a) A deterministic streamline fiber tractography approach was applied on each individual dataset.[188] (b) Seed points were defined at 2 mm isotropic resolution. (c) For defining pathways, the main diffusion direction (as defined by the principal eigenvector) was tracked until entering a voxel with FA <0.20 or high angular turn (angle >45 degrees). The step size was set at 1 mm. (d) The resulting whole-brain fiber tract reconstructions were parcellated using the automated anatomical labeling atlas.[116] (e) Inter-regional connectivity was examined by determining the percentage of tracts (number of fiber connections normalized for the total number of tracts) between any two masks (i.e. any two of 116 regions of the anatomical labeling atlas template). This value became the edge weight in the connectivity matrix. (f) Besides this weighted matrix, an unweighted binary network was constructed with all non zero weights were set to 1 and to 0 otherwise.[189] For every individual data

set, these different kinds of WM networks ('percentage of tracts' and binary) were constructed, each of which was represented by a symmetric 116 × 116 matrix.

The properties of the structural network were investigated at the global and regional (nodal) levels using the Brain Connectivity Toolbox.[190] Standard global connectomics included characteristic pathlength, mean clustering coefficient, global efficiency, small-worldness, normalized path length (λ) and normalized clustering coefficient (γ). Characteristic pathlength measures the average path length in a network, where the path length is defined as the minimum number of edges that must be crossed to go from one node to another (independent of the physical axon length and spatial organization). Mean clustering coefficient is a measure of how many neighboring nodes are also connected to each other, relative to the maximum number of connections in the network. Global efficiency is inversely related to characteristic pathlength: networks with a small average characteristic pathlength are generally more efficient than those with large average characteristic pathlength. Small-worldness represents the balance between network differentiation and network integration. A network is considered small-world if it satisfies the following criteria: γ = mean clustering coefficient / randomized clustering coefficient >> 1 and λ = characteristic pathlength / randomized path length ≈ 1.[191] Here randomized clustering coefficient and randomized pathlength represent were derived from the matched random network created using a modified Maslov's wiring program,[192] which preserves the same number of nodes, edges, and degree distribution as the real brain networks obtained from actual subjects. We also calculated regional efficiency (i.e., global efficiency computed for each node) as a standard nodal connectivity measure.[123]

3.2.7 Statistical analysis

Gender ratio and handedness were compared across groups using chi-squared tests. Two-tailed *T*-tests were used to test group differences in IQ, age standardized scores on the Beery VMI tests, MABC-2, DTI and graph-theoretical network metrics. Pearson correlational analyses were applied to test for possible confounding effects of (P)IQ on Beery VMI outcomes. FA values that significantly differed between groups were also entered in a Pearson correlational analyses against VMI standardized scores in both groups. FA was used as the most important DTI marker in neurodevelopmental pathology and to reduce Type I error.[193] Similar correlational analyses investigated the relationship between regional efficiency and visual-motor impairment. Levels of statistical significance were Bonferroni corrected for multiple statistical comparisons.

Hierarchical multiple regression models were employed within the DCD group to test whether global network metrics (level 2 predictors) were predictive of dynamic visual-motor integration performance (dependent variables) above and beyond specific FA measures (level 1 predictor). In the first step of this approach, FA values that significantly differed between groups were examined in a separate regression model with forced entry. In the second block, a multivariate model with FA and global efficiency measures simultaneously predicting visual-motor integration performance was examined using a stepwise entering method. For each model, we reported changes in R^2 (ΔR^2) to reflect the increase in R^2 before and after global efficiency was entered in the model.

Stepwise discriminant function analysis (with group as outcome variable) was applied to select the most optimal set of predictors from DTI/network metrics for effectively classifying children in the DCD and TD group. Stepwise discriminant analysis enters the most correlated predictor in the first

step. Subsequent steps enter succeeding predictors until they add no significant predictive power to the discriminant function. The initial model consisted of the DTI/network metrics that significantly differed between groups according to the preceding independent *T*-test analyses (Bonferroni corrected for multiple comparisons). The discriminatory power of the resulting model was quantified by its sensitivity, specificity, overall classification accuracy, the Wilks' lambda statistic, and cross-validation.

3.3 Results

3.3.1 Subjects

Twenty-one (17 boys and four girls; mean (M) age 9 years 2 months, standard deviation (SD) = 10 months) children with DCD and twenty (18 boys and three girls; M age 9 years 4 months, SD 7 months) TD children were included in this study. No significant differences measured were present between groups for IQ (DCD: M 109.7, SD 11.0; TD: M 115.6, SD 10.6, p = .090), handedness as defined by the writing hand in the MABC-2 (DCD: 16 right handed, three left handed and two ambidextrous; TD: 16 right-handed, three left handed and one ambidextrous, p = .857), age (p = .742), and gender ratio (p = .623). The mean total percentile score on the MABC-2 was 2.7, SD 1.9 in the DCD group vs. M 52.9, SD 26.3 in the TD group (p < .0001). The applied exclusion criteria were specified in Figure 1.

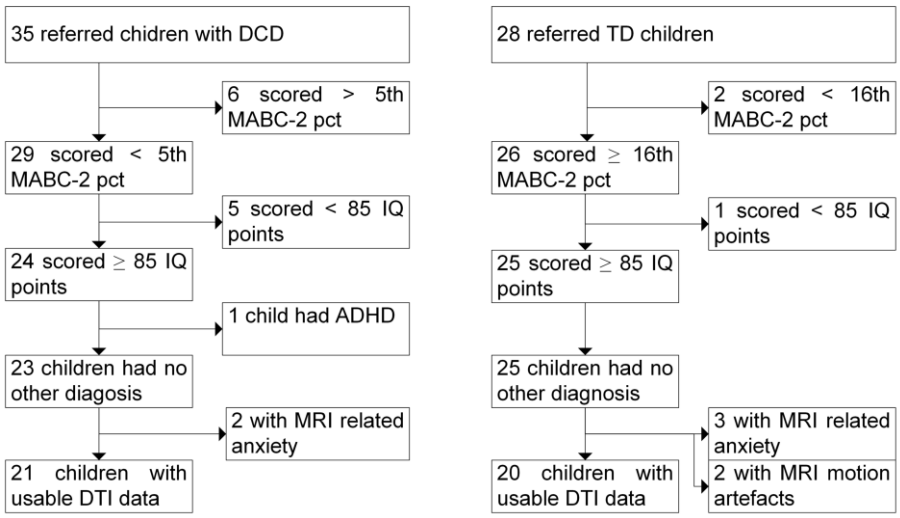

Figure 1. Flowchart of participant selection for the developmental coordination disorder (DCD) and typically developing (TD) group (pct, percentile).

3.3.2 Beery VMI tests

The DCD group scored significantly poorer than the TD group on the VMI copy [t(39) = 7.923, p < .0001], VMI visual discrimination [t(39) = 4.074, p < .0001] and VMI trace test [t(39) = 6.297, p < .0001].

3.3.3 Correlations between Beery VMI and intelligence

Pearson correlational analyses demonstrated no significant correlations between IQ scores on one hand and the Beery VMI copy, or visual discrimination scores. Only one significant correlation was found within the TD group, denoting that better Beery VMI trace scores coincided with a higher PIQ ($r = .599$, $p_{corr} < .006$, Bonferroni corrected). Poor Beery VMI results in children with DCD are hence confirmed to reflect differences fine visual-motor development, without confounding (non-verbal) IQ effects (Table 1).

Table 1 Correlations between Beery VMI and IQ scores

DCD group (n=21)	**VMI copy**	**VMI vis.**	**VMI trace**
TIQ	-.101	.277	.395
	.663	.223	.076
PIQ	.012	.271	.428
	.957	.234	.053
VIQ	.014	.280	.307
	.952	.219	.176
TD group (n = 20)			
TIQ	.144	.303	.268
	.545	.193	.254
PIQ	.209	.347	**.599**
	.376	.134	.005
VIQ	-.039	.188	.164
	.871	.427	.489

$p < .05$ (italic); $p_{corr} < .006$ (bold)
DCD = developmental coordination disorder; TD = typically developing; vis. = visual discrimination; Beery VMI = Beery-Buktenica developmental test of visual-motor integration; TIQ = total intelligence quotient; PIQ = performance intelligence quotient; VIQ = verbal intelligence quotient

3.3.4 Group differences in DTI metrics and correlations with visual-motor scores

The DCD group showed a significant decrease in mean FA (Table 2 and Figure 2) together with an increase in mean RD of the left retrolenticular limb of the internal capsule. A borderline significant lower FA together with a significant higher RD were also observed in the right retrolenticular limb of the internal capsule in the DCD group. Moreover, VMI trace performance significantly correlated

with decreased FA values in the left retrolenticular limb of the internal capsule in the DCD (r = .496, p = .022) and the TD group (r = .530, p = .016), relating worse performance on the tracing task with lower FA values.

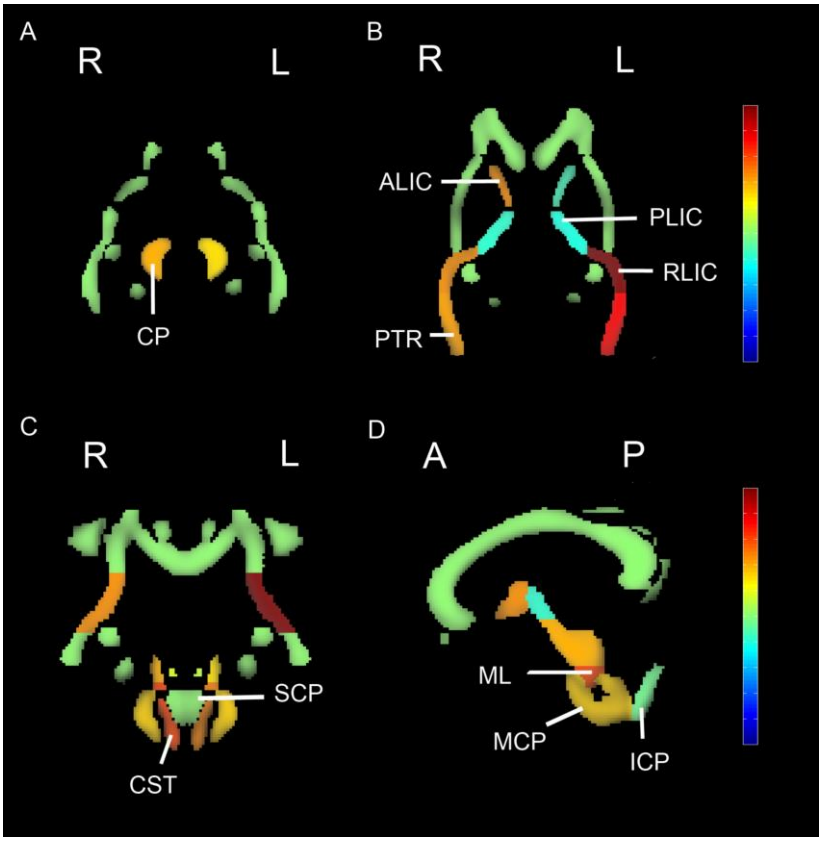

Figure 2. Difference scores in FA between groups for the sensorimotor tracts.
Warmer colors refer to lower FA in the DCD vs TD group. R = right; L = left; A = anterior; P = posterior; CP = cerebral peduncle; ALIC = anterior limb of the internal capsule; PLIC = posterior limb of the internal capsule; RLIC = retrolenticular part of the internal capsule; PTR = posterior thalamic radiation; CST = corticospinal tract; ML = medial lemniscus; ICP = inferior cerebellar peduncle; SCP = superior cerebellar peduncle; MCP = middle cerebellar peduncle

Table 2 Results of the DTI metrics for each ROI in the DCD and TD group

ROI	FA					RD (×10³ mm²/s)					AD (×10³ mm²/s)				
	TD		DCD		*p*	TD		DCD		*p*	TD		DCD		*p*
	M	SD	M	SD		M	SD	M	SD		M	SD	M	SD	
Medial lemniscus L	.578	.033	.564	.032	.189	.427	.020	.443	.037	.094	1.19	.054	1.19	.054	.707
Medial lemniscus R	.578	.031	.565	.037	.242	.439	.028	.455	.035	.110	1.22	.068	1.21	.064	.901
Inferior cerebellar peduncle L	.463	.037	.467	.022	.714	.525	.050	.533	.034	.539	1.13	.097	1.13	.044	.828
Inferior cerebellar peduncle R	.467	.033	.468	.025	.933	.521	.033	.532	.031	.276	1.13	.057	1.14	.046	.394
Superior cerebellar peduncle L	.548	.036	.545	.023	.747	.783	.132	.773	.100	.598	1.78	.014	1.76	.013	.556
Superior cerebellar peduncle R	.538	.035	.533	.029	.671	.808	.124	.788	.110	.785	1.80	.013	1.77	.017	.579
Middle cerebellar peduncle	.500	.016	.490	.014	*.040*	.500	.021	.510	.022	.094	1.13	.025	1.13	.036	.488
Cerebral peduncle L	.632	.029	.623	.024	.150	.458	.034	.465	.023	.493	1.14	.035	1.14	.062	.805
Cerebral peduncle R	.626	.026	.614	.025	.198	.468	.026	.479	.029	.219	1.14	.035	1.14	.061	.444
Anterior limb of int. capsule L	.488	.023	.492	.028	.639	.474	.023	.472	.026	.762	1.10	.038	1.12	.029	.967
Anterior limb of int. capsule R	.518	.020	.504	.028	.077	.455	.017	.468	.024	*.045*	1.13	.033	1.12	.029	.701
Retrolent. limb of int. capsule L	.608	.021	.578	.025	**.001**	.427	.020	.453	.024	**.001**	1.28	.043	1.26	.035	.085
Retrolent. limb of int. capsule R	.574	.025	.560	.024	*.006*	.438	.021	.459	.021	**.003**	1.26	.041	1.24	.048	.220
Posterior limb of int. capsule L	.655	.017	.661	.021	.256	.345	.016	.341	.017	.413	1.19	.029	1.20	.031	.350
Posterior limb of int. capsule R	.655	.017	.660	.023	.434	.352	.014	.349	.018	.569	1.21	.024	1.22	.024	.339
Posterior thalamic radiation L	.572	.028	.550	.029	*.017*	.496	.027	.529	.048	*.011*	1.36	.055	1.36	.047	.922
Posterior thalamic radiation R	.580	.022	.567	.031	.155	.476	.026	.499	.050	.075	1.34	.051	1.34	.042	.588
Corticospinal tract L	.541	.037	.526	.032	.198	.463	.044	.479	.032	.190	1.15	.069	1.14	.047	.690
Corticospinal tract R	.538	.033	.519	.031	.060	.463	.027	.487	.043	*.039*	1.13	.058	1.13	.054	.835

AD = axial diffusivity; DCD = developmental coordination disorder; DTI = diffusion tensor imaging; FA = fractional anisotropy; M = mean; RD = radial diffusivity ROI = region of interest; SD = standard deviation; TD = typically developing
$p < .05$ (italic); $p_{corr} < .003$, Bonferroni corrected (bold)

3.3.5 Small-world topology

Using graph theoretical analysis, WM structural networks of both groups were found to exhibit a considerable higher local interconnectivity of the nodes compared to a random network ($\gamma >> 1$) (DCD group: mean = 3.86, SD = 0.34; TD group: mean = 3.56, SD = 0.21) and an equivalent shortest path length between any pair of nodes ($\lambda \approx 1$) (DCD group: mean = 1.06, SD = 0.02; TD group: mean = 1.07, SD = 0.01), compared with the matched random networks. The small-worldness (γ / λ) calculated from these indices was also above 1 (DCD group: mean = 3.48, SD = 0.31; TD group: mean = 3.33, SD = 0.18). Moreover, the overall normalized path length and local interconnectivity did not differ between DCD and TD children (p's > 0.12).

3.3.6 Global and nodal network parameters and correlations with visual-motor deficits

Lower values of the mean clustering coefficient [t(39) = 2.45, p = .019] and global efficiency [t(39) = 3.60, p = .001] were present in the WM networks of the DCD compared with the TD group. Besides, global efficiency was significantly correlated with VMI trace scores in the DCD group (r = .559, p = .008), with lower global efficiency coinciding with worse tracing performance (p_{corr} = .008) (Figure 3). VMI trace did not significantly associate with global efficiency in the TD group (r = -.80, p = .739).

Differences in nodal efficiency were further investigated between DCD and TD children at p_{corr} = .001. The DCD group showed poorer regional efficiency at the left cerebellum IV-V, bilateral cerebellum VI, left middle cingulum, and right parietal superior gyrus (all p's < corrected level) (Figure 4). Correlational analyses revealed that VMI trace significantly correlated with nodal efficiency of the left cerebellum VI (r = .571, p = .007) in the DCD group. This correlation was absent in the TD group (r = .093, p = .697).

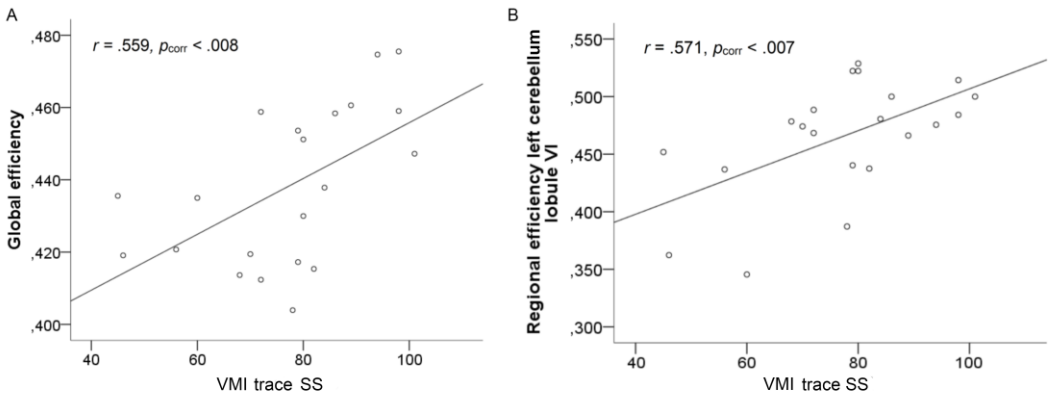

Figure 3. Linear relationships between VMI trace and network metrics.
SS = standardized score

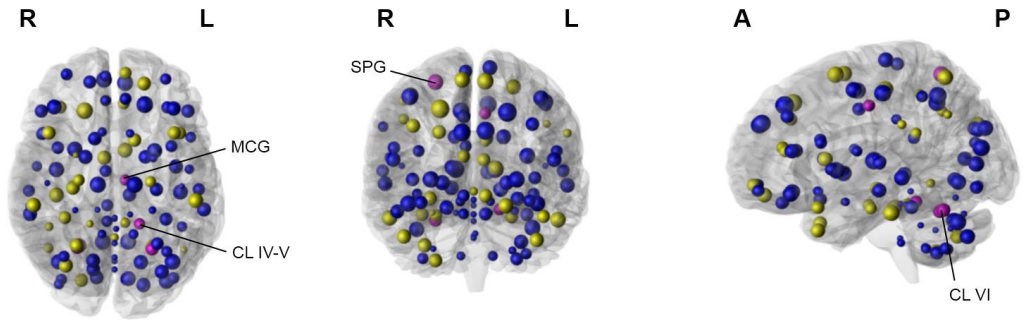

Figure 4. Regional efficiency for the binary network in the DCD vs TD group.
magenta $p < 0.008$ (Bonferroni correction), yellow $p < .05$, blue $p > 0.05$.
R = right; L = left; A = anterior; P = posterior; CL IV-V = cerebellar lobules IV-V; CL VI = cerebellar lobule VI; MCG = median cingulate gyrus; SPG = superior parietal gyrus.

3.3.7 Predictive models of VMI trace using FA and global efficiency measures in DCD

The hierarchical regression analysis revealed that at Step 1, FA of the left retrolenticular limb of the internal capsule significantly contributed to predicting VMI trace scores (Table 3). After Step 1, addition of the independent variable global efficiency in Block 2 to the equation resulted in a significant augmentation in R^2. Global efficiency significantly contributed to the prediction of visual-motor tracing performance. Altogether, Block 2 contributed another 15.7% of the variance in VMI trace scores.

Table 3 Hierarchical multiple regression on Beery VMI tracing performance in the DCD group.

Dependent variable		b	SE b	β	p	Δ R^2
VMI trace						
Step 1						24.6%
	Constant	-87.83	66.26			
	FA RLIC L	283.63	113.8	.496	.022	
Step 2						15.7%
	Constant	-168.50	70.97			
	FA RLIC L	187.50	113.05	.328	.115	
	Global efficiency	311.69	143.04	.431	.043	

3.3.8 Classification models that predict DCD and typical development

Stepwise discriminant function analysis was performed on the DTI/network data to select the most effective set of predictors for distinguishing between the two groups. The initial model included the following DTI/network metrics: FA in the retrolenticular limb of the internal capsule, global efficiency, nodal efficiency at the left cerebellum IV-V, bilateral cerebellum VI, left middle cingulum, and right parietal superior gyrus. The resulting model included 2 predictors: nodal efficiency at the cerebellum lobule VI and the right parietal superior gyrus with a highly significant Wilks' lambda ($p < .0001$), indicating a well-fitting discriminant function.
This two-predictor model achieved a sensitivity of 90.5 % and specificity of 85.0 % in the present group with an overall classification accuracy of 87.8 %. Cross-validation was done using a leave-one-out classification, each case is classified by the functions derived from all cases other than that case. The cross-validation check still gives a 85.4 % classification accuracy. In conclusion, a considerable classification accuracy was obtained from a small set of DTI/network metrics using discriminant function analysis.

3.4 Discussion

This study investigated for the first time the whole brain structural connectomics and associated WM deficits in DCD by means of fiber tractography combined with graph theoretical network analyses.

3.4.1 Alterations in sensorimotor white matter tracts and correlations with visual motor deficits in DCD

FA significantly differed between DCD and TD children in the left retrolenticular limb of the internal capsule. The fibers within convey mainly visual information and lie proximal to sensorimotor loops that subserve coordinated movement.[194] In addition to the group differences, our results indicate that DCD-related FA reductions in the left retrolenticular limb of the internal capsule were associated with deficits in eye-hand coordination, which is consistent with its role in sensorimotor functioning.

Interestingly, pathways with sensory fibers including the retrolenticular limb of the internal capsule and the posterior thalamic radiation have also been found affected in children with cerebral palsy.[195, 196] Our neural findings seem in line with the hypothesis that DCD and (mild) cerebral palsy have similar deficits in sensory pathways and may fall on the lower end of a continuum of neuromotor disorders.[197] This hypothesis was drawn from evidence of cerebral palsy-like neurological soft signs (e.g., mild dysfunction in muscle tone regulation, dysdiadochokinesis, disordered fine motor manipulation) in children with DCD.[198] Nonetheless, the current available data remains insufficient to make inferences of DCD as a kind of minimal cerebral palsy. Further studies should directly compare matched groups of children with DCD and cerebral palsy investigating the possibility of shared symptom-specific neural features.

Our findings contradict with Zwicker's previous DTI study[133] that did not found any FA decreases in sensorimotor WM tracts in children with DCD, possibly due to the small sample size (n = 7). Instead, AD tended towards an increase within the corticospinal tract and posterior thalamic radiation in DCD relative to TD children. The (non-significant) AD increase was hypothesized to signify altered axonal microstructure, which appears unsupported by our findings of non-differing AD values in the DCD and TD group.

The reduced FA consistently co-occurred with significant increases in RD in the bilateral retrolenticular limb of the internal capsule. As previously supported, RD increases underlying the FA decreases is indicative of disintegration of myelin.[199] In this context, myelination degree has been suggested to mediate global brain network topology in children.[200] Our indications of reduced myelination in DCD could therefore implicate alterations in structural brain networks and is discussed next based on graph theoretical analyses.

3.4.2 DCD-related differences in the structural brain connectome

Children with DCD displayed an overall small-world topology which has also been observed in other pediatric studies including healthy children[201] and children with traumatic brain injury (TBI).[186] Despite prominent small-world properties, we identified altered network connectivity in DCD. Specifically, children with DCD relative to the TD group exposed a strong significant decrease in global efficiency, which is the most commonly used measure of functional integration.[202] Moreover, global network efficiency was significantly related to VMI trace outcomes, suggesting that this global connectivity measure yields importance as a biomarker of DCD-related motor problems. Hierarchical regression analysis showed that global network connectivity was predictive of VMI trace above and beyond FA in specific sensorimotor regions/tracts. These results are consistent with a predictive

model in which the global efficiency measure seems to mediate the relationship between FA in specific sensorimotor tracts and figure tracing performance.

Our DCD group also presented a decreased mean clustering coefficient, which implies that DCD affects the local brain network connectivity or organization as well.[186] Confirmed by nodal analyses, the DCD relative to the TD group displayed a decrease in regional efficiency in the left cerebellum lobules IV-V, bilateral cerebellum lobule VI, left median cingulate gyrus, and right superior parietal gyrus as discussed next. The cerebellar lobules with decreased regional efficiency matches with a functional motor control zone, including lobules IV-V, parts of VI and VIII that connect with sensorimotor association cortices.[203] Particularly, the function of cerebellar lobules V and VI involves fine-tuning of motor output by encoding error signals reflecting the difference between expected and observed input.[203, 204] Besides group differences, node-specific correlational analyses performed within the DCD group revealed a significant correlation between the VMI trace score and efficiency of the right cerebellar lobule VI. This accords with the notion that the VMI trace task required optimizing the tracing movement (motor output) in order to draw within the figure lines (sensory input), which in turn involved error encoding (line crossings). Consistent with this, previous functional MRI findings indicated that skilled motor practice of a trail-tracing task associated with under-activation of motor learning networks, including the left cerebellar lobule VI in DCD compared to TD children.[138] Nodal efficiency was also decreased in the left median cingulate gyrus, which contains the so-called cingulate motor areas. These cingulate motor areas are involved in motor control through their direct spinal cord projections and motor cortices.[205, 206] The superior parietal lobule functionally relates to the modification of spatial coordinates depending on attentional priorities (spatial shifting). Evidence suggests that DCD children exhibit abnormal posterior parietal activity during visual-motor tracking, which required adequate selective attention abilities to a dynamic target stimulus.[139] These compensatory activation patterns could result from reduced efficiency in this region.

Concerning the DCD diagnosis, nodal efficiency at the cerebellar lobule VI and right parietal superior gyrus were found significant predictors to discriminate between DCD and TD children with a high accuracy, sensitivity, and specificity. These nodal efficiencies were found to correlate to a moderate degree with VMI trace scores in the DCD group only, whereas similar correlations between local FA decreases (retrolenticular limb of the internal capsule) were not specific to the DCD group as they occurred in the TD group as well.

3.4.3 Methodological considerations and limitations

In this study, the Beery VMI was employed, which is a frequently used and valid clinical test to diagnose visual-motor impairment in children. Despite clear group-differences in line with previous studies,[62, 69] the dependent variables of the Beery VMI only reflect the product of task performance (i.e., the number of correctly copied, identified, and traced geometric figures) and do not allow to infer deficits underlying poor outcomes. A recent meta-analysis of behavioural data demonstrated evidence of several deficits (i.e., motor timing, executive function, predictive control, and sensory-perceptual functioning) that may underlie poor performance on the Beery VMI of children with DCD.[76] Further neuroimaging studies should implement instrumented measures, such as a goal-directed reaching task performed under varying temporal and spatial constraints.[207, 208] These tests

would enable the identification of subtle deficits underlying impaired fine motor skills in children with DCD.

Regarding the imaging procedure, a deterministic tractography approach was employed to calculate DTI metrics and to define the edges of the structural network.[188] Alternative tractography approaches based on the more advanced diffusion models, such as diffusion spectrum magnetic resonance imaging or high angular resolution diffusion imaging with Q-ball reconstruction of multiple fiber orientation may provide more accurate anatomical connectivity patterns.[211] Another limitation of tractography is erroneous tracking results due to noise and resolution limitations.[212] In addition, a deterministic tracking algorithm can only progress reliably when there is a high certainty of fiber direction, limiting their usefulness in reaching parts of the brain close to the gray matter. Finally, percentage of tracts was used to weigh the edges in the calculation of the connectivity matrices and consequently the graph metrics. Other definitions of edge weight, such as FA, level of myelination, and the number of fibers have previously been used.[189, 200, 213] Currently, no consensus is reached on which weighting factor is the most representative measure of structural connectivity. To test the robustness of our results, we also constructed networks weighted by fractional anisotropy and mean diffusivity values. The results of those networks were comparable with those of the presented WM networks (percentage of tracts and binary). Even so, our graph theoretical network analyses remain exploratory because of the relatively small sample size and therefore replication in a larger sample is necessary. Longitudinal studies are needed as well to determine how changes in topological structure of WM networks are related to intervention and motor performance.

3.4.4 Conclusions

This study demonstrates that DCD in children affects the brain's network connectivity with such structural features that associate with deficient visual-motor skills, as well as the DCD diagnosis. Abnormal microstructural characteristics in main WM sensory motor tracts were detected, suggesting deficient myelination development, which in turn may affect network configurations. Indications of a weaker globally integrated structural brain network were obtained by means of graph theoretical analyses. Specifically, decreased global network efficiency significantly contributed to predicting low visual-motor performance outcomes within the DCD group above and beyond FA reductions in the retrolenticular limb of the internal capsule.

The presented method of fiber tractography combined with structural connectomics provides a useful tool for identifying neural features associated with visual-motor disorders in children with DCD. Further large-scale studies are required to focus on developing diagnostic procedures that include optimally discriminating DTI/network metrics to achieve a more objectified identification of the individual child with DCD. Evaluation of treatment is necessary as well in order to quantify rehabilitation effects for remediating topologically suboptimal network configurations in children with DCD.

3.5 Acknowledgments

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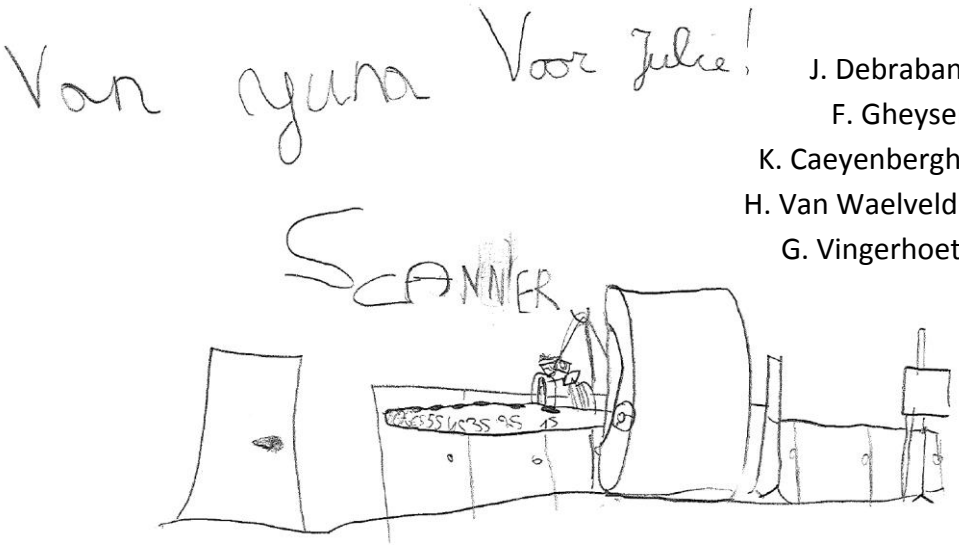
Chapter 4

Neural underpinnings of impaired predictive motor timing in children with Developmental Coordination Disorder



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Research in Developmental Disabilities (2013) May; 34

4 Neural underpinnings of impaired predictive motor timing in children with Developmental Coordination Disorder

Abstract

A dysfunction in predictive motor timing is put forward to underlie DCD-related motor problems. Predictive timing allows for the pre-selection of motor programmes (except 'program' in computers) in order to decrease processing load and facilitate reactions. Using functional magnetic resonance imaging (functional MRI), this study investigated the neural correlates of motor timing in DCD (n = 17) and typically developing children (n = 17). The task involved motor responses to sequences of visual stimuli with predictive or unpredictive interstimulus intervals (ISIs). DCD children responded with a smaller reaction time (RT) advantage to predictive ISIs compared to typically developing children. Typically developing children exhibited higher activation in the right dorsolateral prefrontal cortex (DLPFC) and right inferior frontal gyrus (IFG) for responses at unpredictive as opposed to predictive ISIs, whereas activations in DCD children were non-differentiable. Moreover, DCD children showed less activation than typically developing children in the right DLPFC, the left posterior cerebellum (crus I) and the right temporo-parietal junction (TPJ) for this contrast. Notably, activation in the right temporo-parietal junction (TPJ) positively correlated with RT as an indicator of processing load in both groups. These data indicate that motor performance in DCD children requires extra processing demands due to impaired predictive encoding.

4.1 Introduction

Developmental Coordination Disorder (DCD) is a condition that is characterized by impaired performance in daily activities that require motor coordination (DSM-IV-TR, American Psychiatric Association, 2000).[23] A recent prevalence study reports that almost 2% of all 7-year-old children meet the diagnostic criteria of this condition.[1] The motor performance of children diagnosed with DCD is often described as clumsy in activities like writing, dancing and sports. Their clinical picture shows clear interindividual differences in terms of the severity and diversity of the experienced motor problems, as well as in the co-occurrence of other developmental disorders including attention deficit hyperactivity disorder (ADHD), autism spectrum disorders, or learning disorders.[214] DCD is not associated with a specific pathogenetic cause and is therefore considered to be a clinical label that refers to children with an impaired motor development.[172] In the present study, we focus on the ability of effective motor response timing as one of the underlying difficulties of voluntary motor behaviour in children with DCD.[76]

When motor responses are elicited by an incoming visual stimulus, different sequential processes occur such as stimulus perception, motor programme (except 'program' in computers) selection, motor preparation, and correctly timed movement initiation.[215] Efficient motor responding, which appears problematic in DCD, is enabled by neural systems that attempt to decrease the processing load through predictive coding.[216, 217] This Bayesian predictive coding principle is increasingly supported by recent experimental and clinical findings, and can be illustrated by means of the following example from Körding and Wolpert (2004).[218] When acquiring a motor skill, for instance playing tennis, the perceptual system first provides an imperfect prediction of the ball's velocity in order to be able to hit the ball at the right time. Over the course of practice, a more accurate probability distribution of velocities is set which reduces the error in this estimate. Because the perceptual input can be compared only against the expectations or prior distribution rather than being analyzed from scratch, this predictive model entails a substantial reduction in processing load. However, in children with DCD, the level of motor skill proficiency often endures at the initial practice level. In the example involving ball skills, DCD children continue to fail at effectively catching and/or returning the ball.[84, 86, 87] DCD children do not seem to learn to assimilate the prior distribution of perceptual timing feedback as compared to their typically developing peers. Consequently, processing loads may not reduce despite extensive practice. Moreover, impaired predictive motor responding in DCD not only hampers ball skills, but also accounts in part for deficits in fine motor skills and postural control.[66, 69, 219, 220] Previous studies have assessed predictive motor timing using synchronization paradigms where children were asked to execute finger movements to a rhythmic auditory or visual pacing stimulus.[89-91, 221-223] The key finding of these studies is that children with DCD show increased temporal variability compared with typically developing children.[91]

However, neuroimaging research in DCD remains scarce. To date, only four functional MRI studies have been published, which focused on visual-motor tracking,[139] executive functions,[140] and trail-tracing.[137, 138] Results from these studies suggest that children with DCD exhibit differences in neural network activity and connectivity as compared with typically developing children. Kashiwagi et al. (2009)[139] reported that children with DCD demonstrated lower activation in the left posterior parietal cortex and postcentral gyrus, whereas Querne et al. (2008)[140] showed both increased and decreased functional connectivity in DCD children's executive network including the middle frontal

cortex, anterior cingulate cortex, inferior parietal cortex, and striatal components. Zwicker et al., (2010, 2011)[137, 138] on the other hand, described under-activation in the cerebellar-parietal and cerebellar-prefrontal networks. To the best of our knowledge, no pediatric imaging studies have been performed on predictive motor timing so far.

The present study attempts to fill this gap in three ways. The first aim is to delineate the neural correlates of predictive motor timing abilities in typically developing children. To this end, we used a visual-motor reaction time (VRT) task. In this task, the degree of temporal predictability of the visual stimuli was manipulated by alternating blocks of predictive (regular) and unpredictive (irregular) interstimulus intervals (ISIs). Stimuli with predictive ISIs enable the encoding of temporal information. The temporal error is expected to be small in this condition, which leads to efficient motor reactions (RT advantage). At fully predictable ISIs, the structure of the prior stimulus timing is reinforced. In case of stimuli with unpredictive ISIs, no precise temporal information can be encoded, hence leading to higher prediction errors and less efficient motor responding (no RT advantage). As a result, the prior stimulus timing will be continuously updated as an attempt to better align further temporal predictions.

In this VRT task, children were asked to make a fast response to a stimulus appearing at an expected time (rather than explicit timing judgements). Timing mechanisms are thus engaged automatically (implicitly) rather than deliberately (explicitly).[224] Paradigms that investigate explicit timing demand an estimate of a certain stimulus duration.[225] Neural systems associated with explicit timing involve the dorsal striatum of the basal ganglia with task-dependent co-activation of the supplementary motor area, cerebellum, and prefrontal cortex (for a review, see Coull, Cheng, & Meck, 2011).[226]

In adults, neural correlates of predictive motor timing have been assessed using similar VRT tasks.[151, 152, 227] When contrasting unpredictive and predictive visual pacing conditions (unpredictive > predictive), these studies have reported an increased activation in the dorsolateral prefrontal cortex (DLPFC), the right inferior frontal gyrus (IFG), the posterior cerebellar lobe, and the temporo-parietal junction (TPJ). The relative activation increase in these regions has been related to additional processing and/or updating of priors at unpredictive stimulus pacing. Conversely, well-encoded predictive intervals require less processing as the prior stimulus structure only needs reinforcement. In a previous study, we demonstrated that children's predictive motor timing abilities progress through middle and late childhood.[228] Therefore, similar activations were expected in the DLPFC, right IFG, posterior cerebellar lobe, and right TPJ for responding to unpredictive vs. predictive visual pacing.

The second aim of this study is to compare the resulting activation patterns of typically developing children with those of DCD children, of whom deficient or reduced predictive motor timing performance is expected. It is hypothesized that DCD children lack the ability to make correct prior estimates of stimulus timings, not only at unpredictive but equally so at predictive ISIs. Accordingly, unlike in typically developing children, RTs in DCD children are not expected to be faster at predictive compared with unpredictive ISIs. At the neural level, we hypothesize that the unpredictive > predictive visual pacing contrast is not associated with an activation increase in the aforementioned candidate regions. Because predictive pacing will not induce adequate predictive encoding, neural activations between predictive and unpredictive pacing are expected to be non-differentiable.

Third, in both child groups, we explore in which areas neural activation correlates with visual-motor RT performance which is considered to be a behavioural indicator of processing load.[227, 229] A previous adult study found a positive correlation between visual-motor RT performance and right TPJ activation, suggesting that TPJ activity is related to additional processing of visual-motor information.[227] Therefore, it could be hypothesized that also in children, a higher TPJ activation corresponds to a slower RT performance, reflecting enhanced processing demands.

4.2 Methods

4.2.1 Participants

DCD children between 7 and 10 years were selected from schools for special education and ambulant rehabilitation centres in Flanders, Belgium. For inclusion in the present functional MRI study, children with DCD were required to have a Movement Assessment Battery for Children – Second Edition (MABC-2)[26] score that was ≤ the 5th percentile, an estimated total IQ score of ≥ 85, and no other diagnosed developmental disorders such as ADHD or autism, or medical condition interfering with their motor abilities (DSM-IV-TR).[23] The MABC-2 is one of the most frequently used tests to assess a child's general motor functioning by evaluating manual dexterity, aiming and catching, and balance. The recently translated edition in Dutch, norm-referenced in Flanders and The Netherlands,[230] was used for scoring. The short form of the Wechsler Intelligence Scale for Children – third edition (WISC-III)[177] was used to estimate the child's IQ based on two verbal tests (word similarities and comprehension) and two performance tests (picture arrangement and block design). Out of 35 referred children with DCD, 11 children were excluded because of a MABC-2 score > 5th percentile (n = 5) or an IQ score < 85 (n = 6). In addition, one child had ADHD (n = 1). An additional six children had to be excluded from the final analyses because of claustrophobia and anxiety caused by the scanning procedure (n = 3) or failure to complete the scanning procedure without excessive head movement (> 5 mm; n = 3).

For the control group, 28 typically developing and age–gender matched children were recruited from mainstream schools, identified by their teachers as following normal motor and cognitive development. Data from 2 children were excluded because of a MABC-2 score of percentile 16 (borderline movement difficulties) and from 1 child because of an IQ score < 85. Eight of the 25 remaining children were excluded due to claustrophobia and anxiety (n = 3) or excessive head movement during scanning (n = 5).

In total, 17 DCD children (mean age 9.4 years ± 0.6, 13 boys and 4 girls) and 17 matched typically developing children (mean age 9.2 years ± 0.9, 14 boys and 3 girls) fulfilled the criteria and provided reliable neuroimaging data. No significant differences were present between the child groups for IQ (DCD: 109.4 ± 14.5; typically developing: 116.5 ± 9.6, $p = 0.067$), handedness (DCD: 14 right- and 3 left-handed children; typically developing: 15 right- and 2 left-handed children, $p = 0.628$), age ($p = 0.631$) and gender ratio ($p = 0.680$). The DCD and the typically developing group obtained mean MABC-2 percentile scores of 2.3 ± 2.0 and 53.8 ± 23.2 respectively ($p < 0.0001$). The study was approved by the local ethics committee. Parent consent and child assent were obtained prior to and during all stages of the study.

4.2.2 Experimental task and design

The task was composed using a blocked design, based on previous predictive motor timing studies.[151, 152, 227] The purpose of the task was to react as fast as possible to a centrally placed blowfish cartoon, which was briefly presented (70 ms) against a white background. The responses consisted of pressing a button on a MRI-compatible response pad (CEDRUS lumina, San Pedro, CA, USA) with the corresponding right index finger. All visual stimuli were generated using the 'Presentation' software package (Neuroi.e.al Systems Inc., Albany, CA, USA), and were displayed on a custom-built, shielded TFT screen at the rear end of the scanner visible via a mirror mounted on the head coil. In a predictive visual pacing block, 20 stimuli with fixed ISI of 1200 ms were presented whereas in an unpredictive visual pacing block, stimuli were presented with random ISIs (900–1050–1200–1350–1500 ms; Figure 1). The average pacing rate is identical in both types of visually paced blocks, namely one stimulus every 1200 ms. RTs were registered at the visually paced stimuli. In the experiment, visual pacing task blocks of 25.4 s (i.e., 20 trials) were periodically alternated with self-pacing ('control') blocks. In a self-paced block, participants were instructed to produce a pacing rate similar to the rate in the previous visually paced blocks by repeatedly pressing the response button for a period of 25.4 s. To control for the visual input in the visually paced conditions (blowfish as target), the self-paced condition displayed the blowfish stimulus in response to the motor output (blowfish as response).

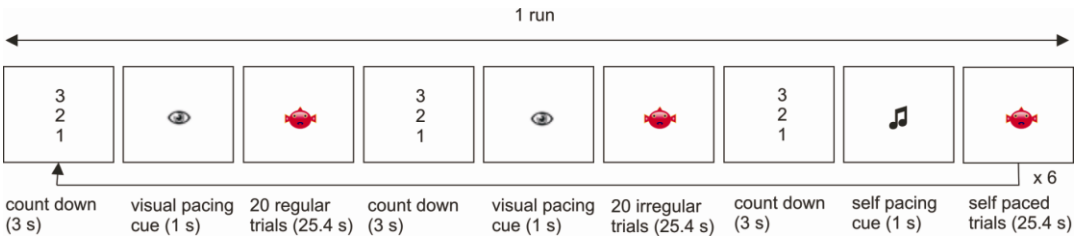

Figure 1. A scanning run included a predictive paced block and an unpredictive paced block followed by a self-pacing block.

The experiment comprised six runs. One run consisted of three blocks, including one of each condition (predictive pacing, unpredictive pacing and self-pacing). The two visual pacing blocks always preceded the self-pacing block, and were counterbalanced across runs and in between subjects. Each block was preceded by a displayed countdown timer of 3 s. A visually paced block (predictive or unpredictive) was initiated by the appearance of an eye symbol (1 s), and a self-pacing block by the appearance of a music note symbol (1 s).

4.2.3 Pre-scanning procedure

Functional imaging studies with children face difficulties such as anxiety, claustrophobia, motion, agitation, and fatigue which make preparation before scanning essential.[231-233] In this study, the following steps were taken to optimally prepare the children. First, the study aims and requirements were introduced to both children and parents in a child-friendly lab environment. MR-safety checklists were assessed prior to scanning. Subsequently, a short practice session (20 trials) for the

VRT task was held with feedback on RT for comprehension and familiarization with the task demands. The visually paced RT task was presented to the children as 'a fish catching task,' and the self-pacing task as 'a rhythm task.' The equipment (head coil, response pad and patient bed) was systematically introduced. After a demonstration, the children had a trial run in the scanner to ensure compliance and cooperation with the imaging procedures. For the children's comfort, animation movies were displayed during the structural MRI acquisition.

4.2.4 Behavioural data analysis

Response time data obtained during the functional MRI experiment were analyzed offline using SPSS Statistics 19 (IBM, Belgium/Luxembourg). Two dependent variables were considered: RT performance (ms) and percentage anticipatory responses (i.e., voluntary motor responses initiated in omission of external sensory guidance typically defined as RT < 100 ms)[163, 234, 235] which were averaged across predictive and unpredictive pacing trials. Predictive motor timing is indicated by an RT decrease and increased anticipatory responses at predictive as opposed to unpredictive ISIs. Group differences in mean RT and mean percentage anticipatory responses were analyzed using linear mixed model (LMM) analysis, with subject as a random factor, group (DCD; typically developing) as a between-subjects factor, and visual pacing condition (predictive, unpredictive) as a fixed factor. Subsequent planned contrasts (Bonferroni corrected with the alpha level for statistical significance set at .006, i.e., .05/8 comparisons) were performed to compare visual pacing effects (predictive, unpredictive) within and between children with DCD and typically developing children.

4.2.5 Functional magnetic resonance imaging

Images were acquired on a 3 T Siemens Magnetom Trio MRI scanner system (Siemens Medical Systems, Erlangen, Germany) using blood-oxygen-level-dependent (BOLD) contrast. An 8-channel phased-array head coil was used for radiofrequency excitation and signal reception. After shimming of the magnetic field, 176 high-resolution anatomical images were collected in the sagittal plane using a T1-weighted 3D anatomical sequence [repetition time (TR) = 1550 ms, echo time (TE) = 2.39 ms, image matrix = 256 × 256, field of view (FOV) = 220 mm, flip angle = 9°, slice thickness = 0.9 mm, distance factor = 50%, voxel size = 0.90 mm × 0.90 mm × 0.90 mm (resized to 1 mm × 1 mm × 1 mm)]. Next 255 whole brain, functional images were obtained in the axial plane for the VRT task using a T2*-weighted echo planar imaging (EPI) sequence [TR = 2500 ms, TE = 27 ms, image matrix = 64 × 64, FOV = 211 mm, flip angle = 62°, slice thickness = 3.0 mm, distance factor = 10%, voxel size 3.3 mm × 3.3 mm × 3 mm, 40 axial slices]. To allow for magnetic field saturation, image acquisition was preceded by four dummy images, which were discharged prior to further processing. All structural MRI scans were screened by a neuroradiologist according to the standard protocol for MRI research.

4.2.6 Imaging analysis

Images were analyzed with Brainvoyager QX 2.3 (Maastricht, The Netherlands) for preprocessing and statistical inference.[236] Whole-brain functional data were subjected to a standard sequence of pre-processing steps comprising slice-scan-time correction by means of trilinear interpolation, 3D motion correction by spatial alignment to the first volume also by means of sinc interpolation, and temporal filtering using linear trend removal and high-pass filtering for low-frequency drifts of three or fewer cycles. Spatial smoothing with a Gaussian filter (4 mm) was applied for the volume-based analysis. The anatomical data for each subject were resampled to a 1-mm resolution and transformed into Talairach standard space using sinc interpolation. The functional data for each subject were co-registered with the subject's 3D anatomical dataset and transformed into Talairach space.

From each run of each subject's paradigm, a protocol file was derived representing the onset and duration of each block for the different conditions. From the created protocols, factorial design matrices were defined automatically. The BOLD response in each condition (predictive, unpredictive and self-paced) was modelled by convolving these neural functions with a canonical haemodynamic response function (gamma) to form covariates in a general linear model (GLM). After the GLM had been fitted at the individual level, group-level analysis was generated using an ANOVA (random effects procedure), including the following factors: pacing condition (predictive; unpredictive; self), between subject factor (DCD; typically developing), and two covariates of interest, mean RT for each subject at each visual pacing condition (predictive; unpredictive).

Entering mean RT performance as a covariate enables a distinction between task-related and performance-related activity.[237] More precisely, the RTs obtained from each subject in each condition were modelled by their level-specific interaction with the categorical factors reflecting each of the two conditions and groups. This design could therefore test for the neuronal activations evoked by the different stimulus timing conditions within each group (DCD; typically developing) independently of those effects that were related to the observed interindividual variations in RT performance. Three sets of analyses were completed. First, focusing on the task effect of predictable timing, one sample t-tests were generated within each child group (unpredictive > predictive and predictive > unpredictive). Second, to test possible activation differences regarding predictable timing, these contrasts were then compared between groups with two sample t-test maps. Third, to identify brain areas related to visual-motor RT performance, the contribution of the covariate RT regressors was tested by contrasting predictive and unpredictive visual pacing conditions vs. the self-paced condition, which allows for controlling visual input as well as motor related activations. An F-test for homogeneous (parallel) slopes tested whether the regression lines are the same for the DCD and typically developing group. The resulting maps were assessed at a statistical threshold of $p < 0.001$, corrected for multiple comparisons with a cluster threshold of 15 contiguous voxels.[236]

4.3 Results

4.3.1 Reaction time and anticipatory responses

Mean RT and mean percentage anticipatory responses are presented in Figure 2A and B, respectively. For both dependent variables, the LMM revealed significant effects for group (DCD,

typically developing) [F(1,32) = 10.621, p < 0.003; F (1,32) = 4.469, p = 0.042] and visual pacing condition (predictive, unpredictive) [F(1,32) = 24.368, p < 0.0001; F(1,32) = 39.713, p < 0.0001], as well as a significant interaction between these two factors [F(1,32) = 6.598, p = 0.015; F(1,32) = 21.368, p < 0.0001]. The typically developing group responded significantly faster at predictive (mean RT = 284 ms and anticipatory responses = 17.88%) than at unpredictive ISIs (mean RT = 385 ms and anticipatory responses = 7.49%) (all ps < 0.0001). In contrast, mean RT and percentage anticipatory responses in children with DCD did not significantly differ between the predictive (mean RT = 412 ms and anticipatory responses = 9.50%) and unpredictive visual pacing condition (mean RT = 439 ms and mean anticipatory responses = 7.90%) (all ps > 0.10). DCD children showed significantly less RT advantage (i.e., RT decrease and increased anticipatory responses) than the typically developing group at predictive ISIs (all ps < 0.0001), while mean RT and mean percentage anticipatory response rates did not differ at unpredictive ISIs (all ps > 0.070).

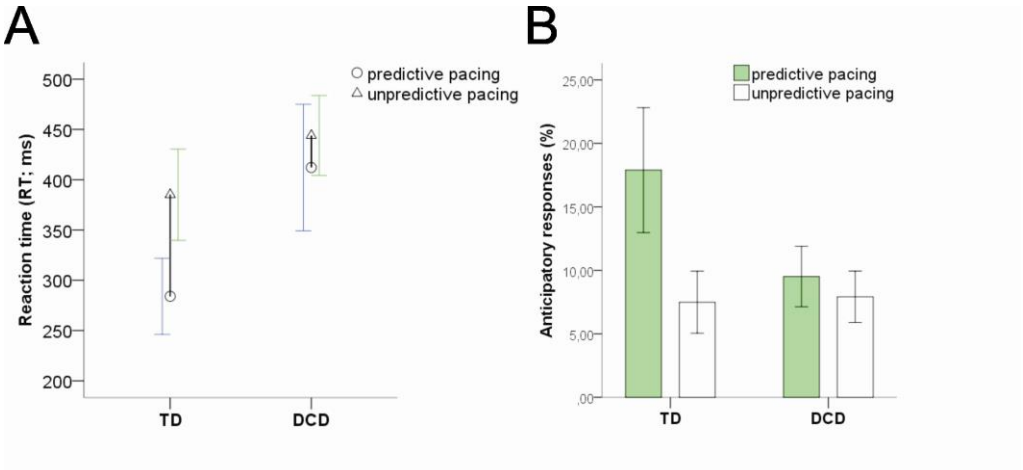

Figure 2. Behavioural data results. (A) Reaction time at predictive and unpredictive visually paced stimuli averaged across runs in DCD and typically developing child (TD) groups. (B) Percentage (%) anticipatory responses at predictive and unpredictive paced stimuli averaged across runs in each child group. Error bars represent 95% confidence intervals.

4.3.2 Imaging data – effects of temporal predictability

Neural substrates of predictive motor timing in typically developing children. As noted above, typically developing children showed a significant difference in mean RT and mean percentage of anticipatory responding between predictive and unpredictive pacing conditions. Accordingly, the neural effects of increased timing uncertainty were localized by contrasting the unpredictive vs. the predictive visual pacing condition (unpredictive > predictive) in the right dorsolateral prefrontal cortex (DLPFC) (middle frontal gyrus) and the right inferior frontal gyrus (IFG). Neither region was associated with reduced timing uncertainty (predictive > unpredictive), that is, they did not show higher activation in the predictive relative to the unpredictive interval condition (Table 1; Figure 3).

Table 1. Talairach coordinates and t values for peak activation in significant clusters ($p < 0.001$ with a cluster threshold of 15 contiguous voxels).

	Contrast	Region	Side	BA	x	y	z	*t*	Voxels
TD	unpredictive > predictive	DLPFC	R	9	35	43	30	5.17	583
		IFG	R	10/11	24	42	6	4.71	140
		IFG	R	47	32	27	-12	4.52	40
	predictive > unpredictive	-							
DCD	unpredictive > predictive	-							
	predictive > unpredictive	-							
TD > DCD	unpredictive > predictive	DLPFC	R	9	32	43	33	4.55	129
		TPJ	R	40	59	-50	30	4.40	25
		Cerebellum (crus I)	L	-	-34	-65	-34	4.21	20
	predictive > unpredictive	-							
DCD > TD	unpredictive > predictive	-							
	predictive > unpredictive	-							

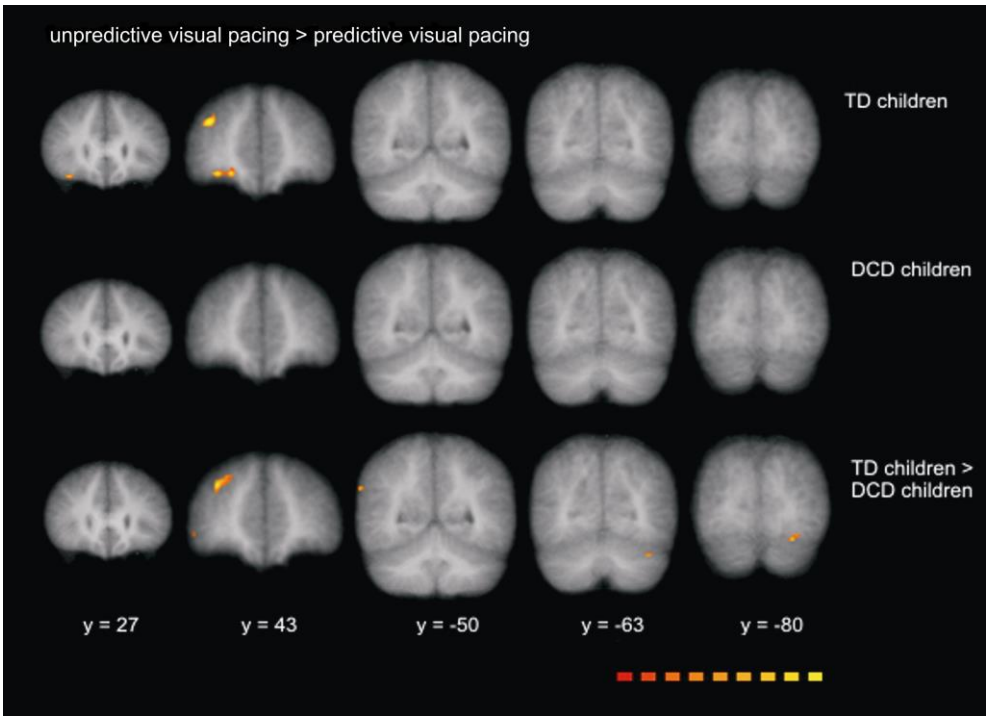

Figure 3. Activity associated with visually paced responses. t-Values show signal change for the unpredictive greater than predictive visual pacing condition (TD: inferior frontal gyrus (IFG), dorsolateral prefrontal cortex (DLPFC); DCD: -; TD > DCD: DLPFC, temporo-parietal junction (TPJ), cerebellum –crus I).

Neural substrates of predictive motor timing in DCD children. DCD children's RTs did not benefit from predictive visual pacing as their RTs did not differ between conditions. In line with the absence of behavioural effects between predictive and unpredictive visual pacing, the 'predictive > unpredictive' and 'unpredictive > predictive' contrasts in DCD children did not yield any significant activations (Table 1; Figure 3).

Differences in neural activation patterns between typically developing and DCD children. For the contrast unpredictive > predictive, typically developing children showed higher levels of activation than the DCD children (typically developing minus DCD children) in the right DLPFC, the left posterior cerebellum (crus I), and the right temporo-parietal junction (TPJ). The opposed contrast (predictive > unpredictive) did not reveal any additional activation differences between the groups (Table 1, Figure 3).

4.3.3 Imaging data: RT correlations

The functional MRI analyses testing for the effect of increased RT (i.e., searching for areas that are more active when children take longer to react) revealed a significant activation at the right TPJ for both the unpredictive visual pacing (vs. self-pacing) (BA 40, 28 voxels, x = 47, y = −44, z = 27, tmax = 3.87) and predictive visual pacing (vs. self-pacing) (BA 40, 18 voxels, x = 50, y = −44, z = 27, tmax = 3.81). No differences between child groups were found for both contrasts, that is, identical slopes of the RT covariate regressors were found between typically developing and DCD children at unpredictive [$F(1,30) = 0.2834$, $p < 0.598$] and predictive visual pacing [$F(1,30) = 0.3257$ $p < 0.572$].

4.4 Discussion

Predictive timing is a crucial component for adequate motor skill performance because it allows for the pre-selection of motor programmes (except 'program' in computers) based on temporal prediction of upcoming events.[227] With a visual-motor RT task, compelling behavioural and imaging results have been obtained in a group of children with DCD and age-gender-matched typically developing children.

Not unexpectedly, DCD children's RT performance did not significantly benefit from temporal regularities in stimulus timing. Furthermore, DCD children responded slower and with fewer anticipatory responses at predictive ISIs, as compared with typically developing children. These findings accord with previous studies, which noted increased temporal error in children with DCD as compared with their peers when synchronizing to a visual or auditory stimulus.[89, 90, 223] Overall, these results support the proposed hypothesis regarding DCD: stimulus timing information fails to be well encoded in order to facilitate the required response and reduce its processing load. Impaired predictive timing in DCD children might relate to a developmental delay since age-related progress has been reported during middle and late childhood.[228] This indication of impaired predictive motor timing corresponds to the more general internal modelling deficit hypothesis in children with DCD.[77, 228, 238-242] Based on self-initiated motor actions a forward model predicts sensory consequences to bypass physiologically slow efferent sensory feedback.[243] From this perspective, a predictive motor timing deficit could explain why children with DCD seem to persist in visually guided online control when responding to predictive stimuli. In contrast, typically developing children more effectively

shift towards a feedforward mode of control, which results in RT advantage. The cerebellar-parietal axis has been proposed as a possible neural correlate of feedforward modelling (see below).[244, 245]

In order to delineate the cerebral regions that are involved in immature systems of predictive response timing, our imaging analyses first focused on the results of typically developing children. In this group higher timing uncertainty (unpredictive > predictive visual pacing) was associated with higher activity in the right DLPFC and right IFG. The contribution of the right DLPFC in motor timing is supported by previous imaging studies. For instance, studies of self-initiated motor responses have shown that the right DLPFC is particularly involved in the free selection of movement timing, a process that requires a decision on when to initiate the motor action.[246, 247] When stimulus timing is predictable, a more automatic response occurs instead of active decision making at unpredictive ISIs. Consequently, the DLPFC may be necessary for making the decision on when to move or withhold movement until the cue. Enhanced timing uncertainty in typically developing children was also associated with increased levels of activity in the IFG. The right IFG has been attributed with a stop signal function for action control.[248, 249] In line with this view, the observed activation in the right IFG might be related to a hold-and-release function. Since children were able to roughly estimate the time of the next trial, but were explicitly instructed to react only once the fish image was presented, they were likely to have prepared the motor action (i.e., button press) earlier, suppressing it until the stimulus appeared.

In DCD children, equal patterns of activation were found for the predictive and unpredictive visual pacing condition, which corresponds with their similar RT performance at both predictive and unpredictive ISIs. Relative to typically developing children, DCD children showed less activity for the unpredictive > predictive contrast in the right DLPFC, the left posterior cerebellum (crus I) and the right temporo-parietal junction (TPJ).

The reduced DLPFC activation in DCD children for the unpredictive > predictive contrast may point to difficulties in response monitoring. DCD children's movement initiation at predictable ISIs seems to rely less on automated responding than that of typically developing children. Similar results were found in another functional MRI study using a go/no-go task in DCD children. Children with DCD were less able to easily switch between go and no-go motor responses.[140] This poor motor response efficiency may be associated with less actively engaging the DLPFC to maintain a high level of response inhibition.[248, 250]

The above-mentioned internal modelling deficit hypothesis might be supported by the decreased activation in the left posterior cerebellum (crus I) in DCD children in case of increased timing uncertainty. The cerebellum has been demonstrated to play an essential role in sensorimotor timing, especially in predictions about time interval duration.[244, 251] The posterior cerebellum (lobule VII, crus I) is found specifically active when participants had to make velocity estimates, and therefore had to incorporate temporal information into their perceptual prediction.[252] These explicit estimates of timing have also been linked with cerebellar functioning in children.[253] However, cerebellar activity (crus I) did not occur in the typically developing child group as a significant neural correlate of predictive motor timing, but only when contrasted with the DCD group. This posterior region of the cerebellum has been associated with cognitive (non-motor) processing[254] and has connections with the prefrontal rather than the motor cortex.[255] In addition, the cerebellum is assumed to participate in an internal timing system. In line with the current study, Dreher et al. (2002)[152] and

Sakai et al. (2000)[151] observed higher activation of the cerebellum in unpredictive as opposed to predictive motor timing. A cerebellar dysfunction or maturational delay has been indirectly linked with DCD by several authors. Besides timing deficits,[66, 69, 89, 90] indications of cerebellar dysfunctions were found in traditional tests, such as the finger–nose test and dysdiadochokinesis.[198]

In addition to the decreased activation of the right DLPFC and the left posterior cerebellum, DCD children showed reduced activation in the right TPJ at unpredictive > predictive visually paced responding, in contrast to typically developing children. This region also featured a significant correlation with longer RTs, and therefore an increased processing load. The BOLD signal was positively correlated with the RT measures to a similar degree in the two child groups. Hence, these results indicate that increased activity in TPJ activity is related to additional processing caused by unsuccessful anticipation, which from a Bayesian perspective would entail a higher prediction error. These results may denote a function for TPJ in the updating of action expectations.[227]

Although this study showed clear neurofunctional deficits in predictive motor timing, additional imaging research in DCD is necessary. For instance, dual task paradigms could be used to further elaborate the processing efforts in children with DCD. During scanning, a rhythmic motor task could be performed as a single task or in concurrence with a simultaneous visual search task (i.e., dual task).[256, 257] In contrast to the single task condition, the dual task condition is expected to induce greater deterioration of motor performance in DCD children and to engage less activation in the right DLPFC, the right TPJ, and the posterior cerebellar regions (crus I), indicating an increased reliance on sensory feedback processing.

Further research should also investigate predictive motor timing differences in children with autism, ADHD, and learning disabilities all of which are neurodevelopmental disorders that often affect motor control and co-occur with DCD.[45, 258] Preferably, a test for sustained attention should be administered, for example a continuous performance test.[89] It is recommended to account for a possible bias in motor timing performance resulting from fluctuations in attention, especially when examining more heterogeneous test groups that include children with ADHD symptoms. It remains to be addressed to what extent beneficial effects of training could be obtained. Interventional studies involving functional MRI sessions pre and post rhythmic motor treatment (e.g., dancing) may be helpful to evaluate neurofunctional plasticity in children with DCD.

4.5 Conclusions

The present study found that motor responses in DCD children, unlike typically developing children, do not benefit from temporal regularities in visual stimuli. Consistent with this, DCD children's patterns of activation did not differ when responding at unpredictive (irregular) and predictive (regular) intervals between stimuli. Typically developing children instead, showed higher activation in the right dorsolateral prefrontal cortex (DLPFC) and the right inferior frontal gyrus (IFG) at unpredictive as opposed to predictive ISIs. For this contrast, typically developing children showed more activation than DCD children in the right DLPFC, the left posterior cerebellum (crus I) and the right temporo-parietal junction (TPJ), while activity in the latter region featured an equally positive correlation with RT as an indicator of processing load in both groups. Consequently, extra processing

efforts are needed in children with DCD to perform visually guided motor reactions. This additional processing can account for the daily motor coordination deficits characterizing DCD.

4.6 Acknowledgments

We are thankful to all the teachers, therapists and children for their participation in this study. We also wish to thank the Centre for Developmental Disabilities, Ghent, Tinneke Hellinckx, and Stefanie Pieters for their assistance in the recruitment.

Chapter 5

General discussion

5 General discussion

The aim of this doctoral thesis was to contribute to the identification of structural and functional neural systems associated with fine visual-motor disorders in children with DCD. This was achieved through a behavioural investigation of visual-motor functioning in typically developing children (Chapter 2) and connecting data from these visual motor tests with DTI (Chapter 3) and functional MRI outcomes (Chapter 4) in children with DCD as compared to matched typically developing children. This general discussion encloses a recapitulation and discussion of our main findings on atypical brain development in children with DCD followed by covering conclusions. From this overview, strengths and limitations, suggestions for future research, and implications with final conclusions are drawn.

5.1 Atypical brain organization in children with DCD

5.1.1 Main findings and discussion

DTI-based tractography and graph theoretical analyses investigated WM structure and whole-brain connectomics in children with and without DCD, engaged in performing the Beery VMI as a clinical test of fine and visual-motor abilities (Chapter 3). FA values were lower together with increased RD in sensorimotor WM tracts of children with DCD. Structure-function relations were also confirmed by positive correlation between FA in the retrolenticular limb of the internal capsule and poor VMI trace outcomes within the DCD group. In addition, reduced global efficiency was shown in DCD, together with reduced nodal efficiency in a number of structures including cerebellum, superior parietal cortex, and left middle cingulum. Specifically, nodal efficiency at the cerebellar lobule VI and right parietal superior gyrus were found significant predictors to discriminate between DCD and TD children. This cluster of findings is consistent with the functionality of the visual-motor task performed by the children, involving the integration of (ordered and recognizable) visuospatial inputs (i.e., geometric figures) into mapped motor responses which preserves the essential elements of the stimulus (i.e., figure tracing).

Interestingly, pathways with sensory fibers including the retrolenticular limb of the internal capsule and the posterior thalamic radiation have also been found affected in children with CP.[195, 196] This preliminary neural evidence supports the hypothesis that DCD and (mild) CP have similar deficits in sensory pathways and may fall on a continuum of movement disorders.[197]

Our consistent findings of decreased FA together with increased RD values suggest deficient myelination in main WM sensory motor tract development, which may in turn have caused suboptimal network configurations. This is in line with Langevin et al. (2014) [134] who registered similar FA and RD alterations in regions of the corpus callosum underlying parietal brain regions, as well as the left superior longitudinal fasciculus in children with DCD. WM integrity was also impacted in both frontal and parietal regions for children with comorbid DCD+ADHD. Zwicker et al.'s (2012)[133] exploratory pilot DTI study found structural alterations in the corticospinal tract that correlated with motor impairment scores. Our results also denoted increased RD in the corticospinal tract (at the uncorrected .05 significance level). FA reductions together with an RD increase are suggested to indicate a delay or deficit in the maturational trajectories of sensorimotor WM in DCD.

The evidence of suboptimal network connectivity in addition to microstructural changes in children with DCD is likely to affect neural activation through visual-motor activities as well. Therefore, compensatory activation patterns were expected to occur in children with DCD as compared to TD children. The functional MRI study in Chapter 4 examined neural activations of predictive visual-motor responding as an underlying deficit of DCD-related motor problems.[62, 76] Predictive timing allows to pre-select motor programs based on temporal predictions of upcoming events that facilitate motor performance. Adequate motor timing hence enables fine-tuned and anticipatory reactions at temporally predictive (i.e., regularly paced) sensory stimuli relative to unpredictive (i.e., irregularly paced) ones. The RT advantage at sequences of predictive visual stimuli was found a significant predictor of fine motor tracing abilities in typically developing children as tested with the Beery VMI (Chapter 2).[228] Poor drawing and writing performance in children with DCD are therefore likely to result from erroneous "starting and stopping" (e.g., overshoot errors) rather than improper rotation, integration, or distortion.

As hypothesized, children with DCD showed only limited RT advantage at predictive stimuli as compared to typically developing children using a visual-motor reaction time test. At the neural level, typically developing children exhibited decreased activation in the right dorsolateral prefrontal cortex and right inferior frontal gyrus, indicating facilitated and speeded responding at predictive as opposed to unpredictive stimuli. Contrary, activation patterns did not differ in children with DCD for motor responses at predictive visual stimuli due to compensatory processing from poor predictive encoding. In addition, the right temporo-parietal junction positively correlated with unpredictive RT rates as an indicator of processing load in both groups of children.

This functional MRI study revealed that motor responding resulting at regularly paced sensory stimuli does not give rise to performance improvements in DCD children as opposed to typically developing children. Consequently, children with DCD must encounter extra processing efforts to perform sensory guided motor reactions, consistent with clinical observations of these children when involved in motor-based activities. Our study agrees with previous functional MRI studies in children with DCD that denote significant compensatory activation while performing visual-motor tasks, such as visual-motor tracing and tracking.[137-139] Our functional MRI study adds to these findings by targeting a specific underlying processing deficit, i.e., predictive motor timing. Similar paradigms for functional MRI have been applied to disentangle the neural substrate of motor timing abilities in adults[151, 152, 227] and children with ADHD.[258] This allowed for a rather hypotheses-driven instead of an exploratory study of aberrant activation patterns in DCD. As expected, aberrant activation in the cerebellar crus-I region, IFG, DLPFC, and TPJ was confirmed in children with DCD. This resembles with results in individuals with ADHD who display comparable motor timing deficits in terms of increased RT variability and decreased benefit in RT at predictable intervals. [258] Compelling evidence shows deficiencies in networks mediating timing functions in ADHD.[259] Children and adolescents with ADHD are also found to have diminished cerebellar and IFG activity to violations of stimulus timing relative to matched controls.[259] The deficits in the left DLPFC furthermore were associated with enhanced intraindividual RT variability in individuals with ADHD, thought to reflect poor concentration and poor stimulus anticipation.[260, 261] These findings support the idea of a partly shared neurobiological basis underlying DCD and ADHD (cf. 5.3.1). Alterations in predictive motor timing in individuals with ASD are likely as well, given their general deficiency in time-related skills[262] and especially because of substantial cerebellar abnormalities, i.e., increased volume and decreased numbers of Purkinje and granular cells.[263, 264]

5.1.2 Covering conclusions

Our studies found convincing evidence of atypical brain organization underlying fine visual-motor impairment in children with DCD. The structural alterations suggest reduced myelination in main WM sensory motor tracts, which may in turn cause suboptimal network configurations. These structural features associated with visual-motor deficits and the DCD diagnosis. As a result, diffusion MRI based metrics hold clinical potential for diagnosing DCD.

Neural activations from fine visual-motor activities were altered as well and may compensate for deficient predictive control abilities in children with DCD as compared to typically developing children. From our findings, it can hypothesized that these compensatory activations originate from suboptimal structural networks supportive of fine visual-motor functioning.

5.2 Strengths and limitations

The studies included in this thesis have progressed in identifying patterns of brain abnormalities present in children with DCD. However, our results remain preliminary due to the small group size and restricted participant in- and exclusion criteria which limit generalizability to the entire DCD population (Figure 1). Our studies included children with DCD without other diagnosed developmental disorders or medical conditions that could interfere with their visual-motor abilities. However, DCD frequently co-occurs with other developmental disorders.[2] Future studies may be conducted to investigate whether findings can be replicated in a more representative group of children with DCD including those with co-occurring developmental disorders. The MRI scanning procedure itself caused substantial participant drop out. Up to 5 % of the selected children with DCD and 20 %of the controls were excluded due to scanning related fear or motion artefact from excessive head movement in the DTI data. These numbers augmented to respectively 26 % and 32 % for the functional MRI session, despite our efforts of comforting and preparing the children prior to the scanning (cf. 4.2.3). Therefore, using a MRI simulator is recommended to improve data quality and minimize data loss.[231-233]

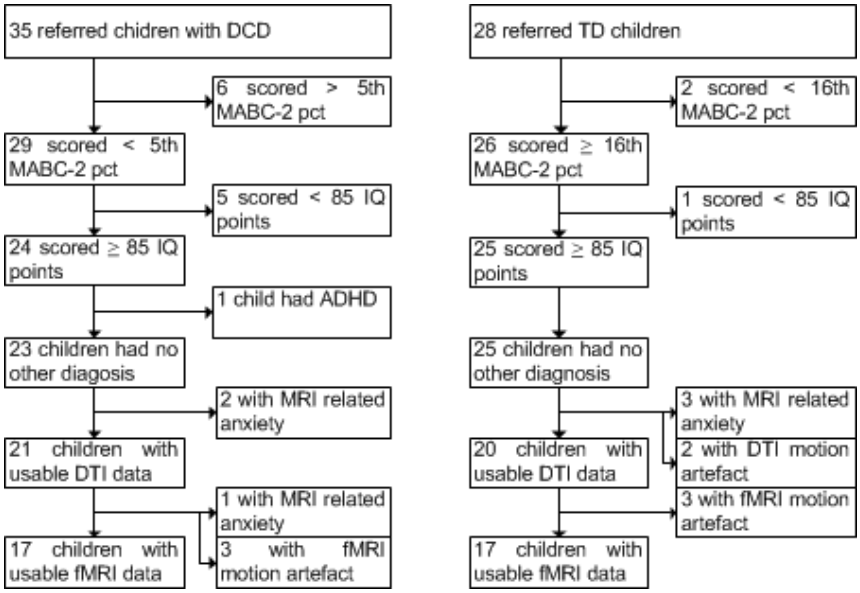

Figure 1. Flowchart of participant selection for the DTI and functional MRI study (pct, percentile).

Neuroimaging has revolutionized our understanding of neurodevelopmental disorders on brain structure and function in vivo, including the tracing of developmental trajectories in children and adolescents. Despite continuing technical advances, MRI modalities remain restricted to spatial and temporal resolutions to enable visualizing the synaptic or neuronal-level abnormalities that may be core features of DCD and other disorders. Nevertheless, neuroimaging combined with tissue analysis and animal models, is likely able to uncover critical associations between risk factors such as specific genes and behavioural symptoms and improving our knowledge on pathophysiology.[265]

5.3 Future research perspectives

In this section, a couple of directions are specified for further investigation based on our findings and the current literature. These outlined directions comprise the degree of convergence between visual-motor impairment and shared neural features between DCD and other developmental and genetic disorders. Next, morphological analyses on T1-weighted MRI data could enhance findings on structural brain features related with DCD. Finally, large-scale studies need to focus on developing diagnostic procedures that include the most optimal discriminating MRI metrics to achieve a more objectified identification and treatment evaluation of the individual child with DCD.

5.3.1 Visual-motor skills in other developmental and genetic disorders

DCD frequently co-occurs with additional developmental disorders. Studies have demonstrated high degrees of comorbidity between DCD, ADHD, ASD and learning disabilities. For instance, up to 50% of children with DCD show to also meet criteria for ADHD,[266, 267] Evidence also suggests that one-third of children with speech and language impairment are likely to have DCD.[268, 269] Other medical conditions such as benign epilepsy of childhood with centrotemporal spikes syndrome,[270] joint

hypermobility syndrome,[271] and neurofibromatosis type 1 (NF1)[272] have also been associated with DCD.

Similar motor phenotypes among developmental and genetic disorders are likely to have a certain degree of shared etiology and neuropathology. Kaplan et al.[273, 274] described a model for co-occurring multiple developmental problems as 'atypical brain development.' This concept underlines the interrelatedness of developmental disorders and the possibility of multiple developmental features (e.g., ADHD, motor coordination problems, and/or ASD) stemming from common dysfunction in brain systems subsequently affecting a number of brain processes, rather than co-occurring problems resulting from multiple etiologies.[274] In support of this, recent evidence suggests that certain genes may increase the risk of DCD, ASD, and ADHD. Significantly overlapping linkage peaks were detected in genome-wide scans of ADHD and ASD.[274] Moreover, two of the four ADHD–ASD linkage overlap regions show evidence of linkage for atypical cerebral laterality. Cerebral laterality may therefore influence both ASD and ADHD, particularly in individuals manifesting more severe motor coordination issues.[274] Further investigation is required to identify possible trans-diagnostic symptoms and their respective neurobiological markers. The identification of shared and distinct etiologies for concurrent neurodevelopmental disorders represents a critical step in providing earlier diagnosis and intervention.

5.3.2 T1-weighted MRI-based brain morphometry

Morphological analyses need to be applied on T1-weighted MRI scans to further investigate structural brain features related with DCD. Resulting regional morphometrics include the cortical thickness, volumes of cortical grey matter, cortical-associated WM regions, and subcortical structures. Additional network (correlative) metrics, which convey the morphological change pattern between pairs of regions, can also be derived using graph theoretical analyses (cf. 1.2.3). These network metrics are presumed to represent higher order information of disease pathology. Abnormalities in network connectivity have been found to associate with ASD[275, 276] and ADHD[275] with distinct large-scale connectivity patterns as well as some shared biological features attributed to frequent comorbidity.[275]

For instance, a recent study demonstrates that the integration of regional and network morphological features can significantly improve the classification performance of ASD and typically developing children, compared with using either regional or network morphometrics separately.[276] Specifically, the proposed model achieved a classification accuracy of 96.27% and an almost perfect AUC (area under the receiver operating characteristic curve) value, indicating excellent diagnostic power and generalizability. This exemplary ASD study suggests that predictive models integrating regional and network morphometrics may as well provide a useful approach for achieving greater sensitivity to the neuropathologies associated with DCD.

5.4 Implications and final conclusions

5.4.1 Clinical implications

In clinical settings, DCD is a frequently underestimated neurodevelopmental disorder that lacks a concrete neurological basis. This apperception seems to persist notwithstanding convergent

evidence of differences in brain structure and function between DCD and typically developing children. Our DTI/network metrics obtained promising results for classifying DCD and typically developing children. Using only two DTI/network metrics (nodal efficiency at the cerebellum lobule VI and the right parietal superior gyrus; N = 21), the model obtained a classification accuracy of 87.8 %with a sensitivity of 90.5 % and specificity of 85.0 % (Figure 2A). In comparison, a classification model with behavioral RT indices (processing speed and predictive timing; N = 17) achieved a classification accuracy of 85.3 % with a sensitivity of 94.1 % and specificity of 76.4 % (Figure 2B). To achieve more clinical impact, the development of highly accurate predictive models is needed to identify children with DCD from typically developing ones, with replicable results across scanners and subjects.

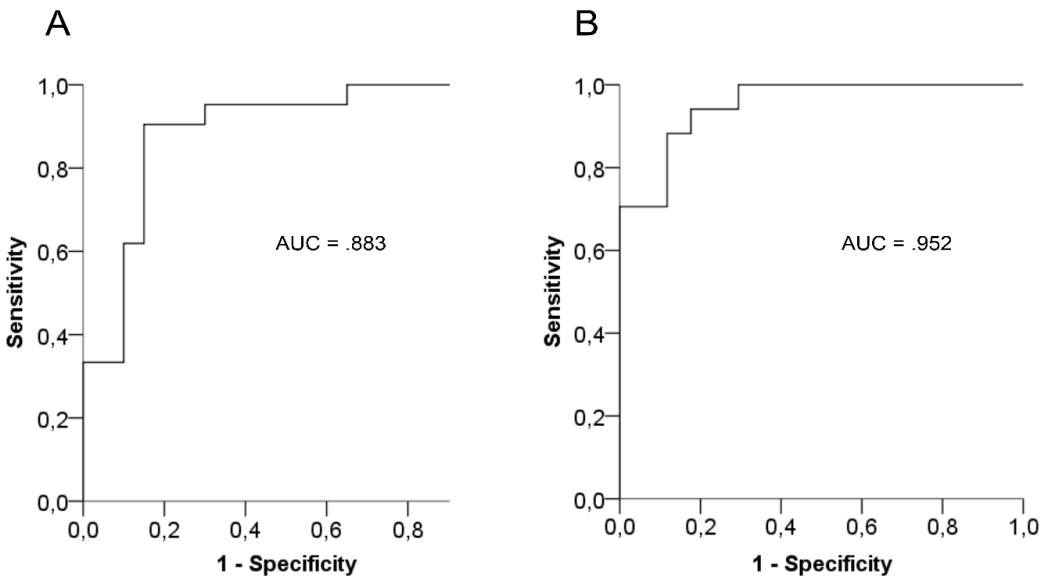

Figure 2. ROC curve and area under the curve (AUC) using DTI/network metrics (A) and behavioral reaction time (RT) measures (B) for classifying children with DCD.

Currently, insufficient research has been conducted and biomarkers with diagnostic value on an individual level have yet to be determined. The adoption of multimetric methods is required to reflect the widespread and subtle structural and functional differences that will likely occur with larger scale studies.[277, 278] The difficulty with this approach however, is the use of DCD as a discrete entity. Although, providing a diagnostic label and indications for intervention can be highly useful from a clinical perspective, the DCD phenotype is more likely to represent a set of continuous deficits that extend into the general population, without definite edges to other disorders such as ADHD and ASD.[279] DCD labels individuals whose expression of a particular set of motor symptoms has reached a level of severity affecting daily functioning and quality of life. The DSM-5[2] holds on to this categorical diagnostic system, acknowledging its clinical utility and the lack of sufficient evidence to support more substantive revision. However, for research purposes, increasing assertion is noticed for reducing the emphasis on categorical diagnoses.[280] Promising alternatives include transdiagnostic dimensional approaches, which focus on specific deficits (for example, response at

visual stimuli, or inhibition) as a more feasible to link across multiple levels of neural, motor, cognitive, and behavioural functioning regardless of which clinical disorder or syndrome diagnoses.[281-283] Moreover, this approach implicates performance levels in typically developing children and elite performers as well. To date, little is known about within-child stability; that is, to what degree performance varies as a function of specific maturational, and/or environmental factors. Clearly longitudinal data is essential to inform these broader issues of development.

Another difficulty regarding behavioural based diagnostics is that the clinical motor tests miss sensitivity since a number of children with DCD achieves to obtain age-appropriate motor performance scores through compensatory strategies. Dysfunctional motor behaviour therefore, entails an additional qualitative examination by trained and experienced clinicians, which is more prone to subjective interpretation. In these cases especially, it would be highly interesting to be able to check for neural indications of DCD motor behaviour using MRI procedures as objective measurement.

Our findings together with recent systematic reviews suggest recommendations for intervention research.[76, 284] These studies should focus on effective ways to improve predictive control as required for rhythmic coordination and timing within and between limbs. When concurrent augmented feedback is provided in synchrony with voluntary, rhythmic movements, the stability of coordination is often enhanced.[285, 286] This modality and its beneficial effects on motor performance however require further investigation in DCD.[76] Temporal cues such as rhythmic perceptual patterns are already applied in psycho-motor intervention programs. For example, Le Bon Depart method applies external rhythms from music or metronomes to support children's graphomotor control.[287] The ability of temporal encoding allows to preselect motor programs and enhances fluent handwriting. Clinical trials could further evaluate rhythmic cueing effects in the treatment of visual-motor control limitations in children with DCD. Future studies using imaging markers of DCD need to focus on individual diagnostic and prognostic classification, as well as treatment evaluation for reversing those structural (i.e., demyelination of main sensorimotor tracts) and functional brain abnormalities.[288]

5.4.2 Research-related implications

Out of the different imaging modalities, structural MRI (DTI and T1 weighted) is the most promising for advance brain based diagnostic indicators of DCD due to fast acquisition speed. Because of its ability to detect the anatomical brain abnormalities, structural MRI may add objectivity to behavioural assessment in diagnosing DCD in the individual child. Another advantage entails the option of attaining structural MRI in very young children as an entirely safe and painless procedure, only requiring sedation for relaxation. Early diagnosis is of great clinical interest as well, since DCD-related motor problems are likely to improve by means of treatment at toddler age,[60, 289, 290] which in turn may improve quality of life while growing up. At this point in time, neither the required type and amount of motor treatment is known to induce neuroplastic changes, nor training to facilitate predictive motor control in children with DCD.[3] Combined structural and functional MRI based interventional studies can provide tools to evaluate effective treatment interventions in remediating associated suboptimal neural network configurations.

5.4.3 Final conclusions

In this thesis, novel findings have been presented to differentiate children with DCD from typically developing controls using structural and functional MRI. The structural alterations suggest reduced myelination in main WM sensory motor tracts, which may in turn cause suboptimal network configurations. Specific structural features of DCD have been correlated with visual-motor performance using valid clinical tests, resulting in convincing brain-behavioural associations. Consequent aberrant functional activation provides supportive evidence of DCD as a neuromotor developmental disorder that is closely related to impaired predictive visual-motor control. The reliability and robustness of our findings requires further evaluation in subsequent large-scale studies to determine DCD-associated biomarkers that can be incorporated in diagnostic and treatment evaluations.

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